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Impact of Depression on Clinical Outcomes Following Percutaneous Coronary Intervention - A systematic review and meta-analysis

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ABSTRACT

Objectives The objective of this meta-analysis was to assess whether depression in PCI patients is associated with higher risk of adverse outcomes.

Design Systematic review and meta-analysis.

Methods PubMed and EMBASE were searched as data sources. We selected prospective cohort studies evaluating the relationship between depression and any adverse medical outcome, including all-cause mortality, cardiac mortality, and non-fatal events, from inception to April, 2018. Two reviewers independently extracted information and calculated the risk of cardiovascular events in patients with preoperative or postoperative depression compared to non-depressed patients.

Results Eight studies (N=3,297) met our inclusion criteria. Most studies found a positive association between depression and adverse cardiovascular outcomes. Meta-analysis yielded an aggregate risk ratio of 1.57 (95% confidence interval 1.28 – 1.92, P<0.0001) for the magnitude of the relation between depression and adverse outcomes.

Conclusions: Our systematic review and meta-analysis suggests that depression is associated with an increased risk of worse clinical outcome or mortality in patients undergoing PCI. Assessment time and length of follow-up do not have a significant effect on this conclusion.

Keywords: depression; percutaneous coronary intervention; prognosis; meta-analysis

Strengths and limitations of this study

1. This study emphasizes the growing recognition that depression is a major risk factor of cardiovascular disease.
2. Depression needs to be fully considered when assessing the prognosis of PCI patients.
3. The quality of the included studies was relatively high.
4. Further analyses were difficult to conduct due to the limited number of studies.

1. INTRODUCTION

Depression is common in patients with cardiovascular disease (CVD) and has been identified as a risk factor for coronary artery disease (CAD). Depression and coronary artery disease are highly comorbid conditions with estimates of comorbidity from 20% to 50%[1-3]. Patients with a combination of depression and CAD are at increased risk for negative cardiac outcomes. Prior meta-analyses have demonstrated that depression is associated with a 2−4-fold increase in the risk of future major adverse cardiovascular events in post-myocardial infarction (MI) patients, and this relationship has remained stable despite improvements in diagnosis and treatment[4, 5]. The adverse effects of depression are also observed in patients admitted with unstable angina[6].

Percutaneous coronary intervention (PCI) has become a common revascularization procedure with demonstrated safety and efficacy. Nonetheless, the prevalence of depressive symptoms increases significantly during the perioperative period[7], and psychological factors like depression and anxiety predict adverse cardiac events post-PCI. However, several studies have suggested that depression was not associated with long-term mortality following PCI[8, 9]. Considering these mixed results, we performed a systematic review and meta-analysis to determine the prospective relationship between depression and adverse clinical outcomes after PCI.

2. METHODS

A systematic review and meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10]and a priori study protocol.

2.1 Search strategy and selection criteria

Two authors (Wen Yi Zhang and Nan Nan) independently searched the literature in PubMed and EMBASE databases without language restriction from inception to April 2018. The search strategy contained keywords related to the population of interest (CAD patients receiving PCI) and keywords related to depression. In PubMed, we used the combination of Medical Subject Headings (MeSH-terms) and relevant free-text terms to identify keywords for each topic. The set operator AND was utilized to form a complementary search strategy (See Box 1). The search terms from PubMed were adapted to the corresponding vocabulary of EMBASE.

2.2 Selection and Exclusion Criteria

Studies investigating the association between depression and prognosis in patients receiving PCI were retrieved for review. Inclusion criteria were as follows: (1) prospective design, (2) patients diagnosed with CAD and receiving coronary stent implantation, (3) using established assessment instruments or structured clinical interviews to define major depression or depressive symptoms, and (4) reporting an endpoint of all-cause mortality, cardiac mortality, re-hospitalization, or major adverse cardiac events (MACEs).

The exclusion criteria were as follows: (1) case report, animal research, review

article or expert opinion, (2) depression not considered as a predictor, (3) unrelated to the search terms, (4) participants without PCI, and (5) data were not reported. For multiple publications from the same cohort[11-15], we chose the latest or most complete study for assessment[12].

2.3 Data extraction

Two authors independently (Jin Fan Tian and Xue Yao Yang) read the abstract and title of every record identified by the search. Potentially eligible studies were reviewed in detail. Differences in opinion were resolved by consensus. Given that a variety of factors may influence outcome, the following data were extracted from the final eight studies: first author's name, study design, ethnicity of the study population, diagnosis of CAD, depression measurement, timing of assessment, outcome definition, length of follow-up, sample size, and number of patients in the depressed and non-depressed groups.

2.4 Quality assessment

We used the Newcastle-Ottawa Scale[16] for quality assessment of included studies. The Newcastle-Ottawa Scale grades three domains: the selection of participants, comparability of the groups, and assessment of outcome[16]. A study can be awarded a maximum of 9 stars for quality. Each study was assessed independently by two investigators. The results are reported in Table 1.

2.5 Data synthesis and statistical analysis

Review Manager (RevMan) (Version 5.3, The Cochrane Collaboration, 2014) served as the statistical platform for data management and statistical analyses. Dichotomous frequency data were extracted from each study. Risk ratios (RRs) were calculated from pooled data comparing depressed and non-depressed groups for the likelihood of adverse cardiovascular events. We calculated a pooled RR and 95% confidence interval (95%CI) in the random effects model to account for possible methodological and clinical heterogeneity.

2.6 Heterogeneity Analysis

The statistical heterogeneity among studies was evaluated using the Cochran's Q test, I^2 statistic, and degrees of freedom. The Q test was used to estimate test heterogeneity among trials. The Q value can be used to derive the I^2 value, which is the proportion (%) of variance in a pooled effect size due to heterogeneity rather than chance. Based on I^2, heterogeneity was rated as low (I^2<50%), moderate (50%−75%), or high (>75%)[17].

2.7 Publication bias

Publication bias was assessed by means of Egger's regression asymmetry test[18] and Begg's test[19]. We used the funnel plot to examine whether sample sizes influenced the results of the meta-analysis.

2.8 Sensitivity analysis and subgroup analysis

To further explore the sources of heterogeneity, we conducted a sensitivity analysis by omitting one study at a time and calculating the pooled effect size, 95%CI, and heterogeneity of the remaining studies (Table 2).

We conducted subgroup analyses to assess possible moderator effects for the association of depression with prognosis after PCI. These moderator effects included the time point for evaluating depression, the type of outcome, and length of follow-up.

2.9 Patients and public involvement statement

The patients or public were not involved in the study.

3. RESULTS

3.1 Study selection and description

A flow diagram of the literature search is illustrated in Figure 1. A total of 1,432 records were identified through the literature search, with 1,272 articles remaining when duplicates were removed. These articles were evaluated in detail. Ultimately, eight studies met the inclusion criteria and were included in the meta-analysis[8, 9, 12, 20-24]. The included studies were published between 2011 and 2018, and had follow-up periods ranging from 1 year to 10 years. Sample size ranged from 125 to 1,112, and the eight studies included a total of 3,297 participants from the Netherlands, China, Korea, Brazil, and Germany. The quality of the studies was good, with four of eight studies (50%) rated 9 stars on the Newcastle-Ottawa Scale.

Four of the eight studies defined depression according to the Hospital Anxiety and Depression Scale (HADS) [25]. The level of depression was considered clinically relevant at a cut-off HADS score of 8. Wang et al. (2013) used a combination of HADS and the Mini-International Neuropsychiatric Interview (MINI) to identify patients with depression. Yu et al. (2017) used the 9-question Primary Care Evaluation of Mental Disorders brief patient health questionnaire (PHQ-9) to define depression (non-depressed ≤ 4, depressed 5−27). Schmidt et al. (2011) identified patients with depression using the Beck Depression Inventory (BDI) with 20 points as the cutoff value. The study by Li et al. (2012) defined depression according to the Zung Self-Rating Depression Scale (Zung SDS).

Two studies reported all-cause mortality, four studies reported adverse cardiac events as an outcome, and two studies reported both all-cause mortality and adverse cardiac events separately[9, 24]. MACE was defined according to the individual studycriteria and included all-cause mortality, nonfatal MI, revascularization (as evidenced by repeated PCI, target vessel revascularisation [TVR], target lesion revascularization [TLR], or coronary artery bypass graft [CABG]), and re-hospitalization with cardiac death. Specific characteristics of the included studies are summarized in Table 1.

3.2 Meta-analysis results

3.2.1 Effect of depression assessed at any time on composite outcome

For the pooled sample (eight studies), depression assessed at any time period

resulted in a significant increase in the incidence of cardiac events (risk ratio = 1.57, [95%CI] 1.28–1.92) in the random effects model, indicating that depressed individuals have a 57% greater risk of poor outcome than non-depressed patients. The overall results are displayed in Figure 2.

3.2.2 Depression and all-cause mortality as an outcome

As shown in Figure 3, in the sub-analysis of four studies that included all-cause mortality as an outcome, depression was associated with a significantly higher risk of death after PCI (RR = 1.43 [1.24−1.65]).

3.3 Sensitivity analysis

To determine the reliability of the results, sensitivity analyses were performed by omitting one study at a time. No individual study had a substantial impact on the pooled effect size and heterogeneity. The RR changed slightly only when excluding the study by Dijk et al. (2016)[12] with the largest number of participants (RR = 1.67 [1.26−2.21]) (see Table 2).

3.4 Publication bias

The funnel plot demonstrated slight asymmetry (Figure 4), suggesting that there may be unpublished studies which have found no relationship between depression and clinical outcomes. However, neither Egger's test nor Begg's test revealed evidence of publication bias ($p > 0.1$), although these results should be interpreted with caution due to the limited number of included studies.

3.5 Subgroup analysis

3.5.1 Subgroup analysis by depression assessment time

The pooled RR was also calculated for studies assessing depression during hospitalization and for those measuring depression 2 weeks or more after PCI. For studies with depression assessed in hospital, the RR = 1.71 [1.06−2.73] and for those with depression evaluated 2 weeks or more post-PCI, the RR = 1.65 [1.30−2.08] (Figure 5).

3.5.2 Subgroup analysis by follow-up time

We used 3 years as the cut-off for distinguishing short- from long-term follow-up to evaluate whether the prognostic value of depression for predicting adverse outcomes was temporally limited. The pooled RR for studies with follow-up time less than or equal to 3 years was 2.09 [1.58−2.76], whereas the increase in risk became less pronounced when examining composite outcomes with longer follow-up times (RR = 1.38 [1.20−1.60]) (Figure 6).

3.6 Heterogeneity

Heterogeneity across studies was determined to test the appropriateness of combining studies. Slight heterogeneity was apparent among all included studies (I^2=35%, p for heterogeneity = 0.15). However, heterogeneity remained low (I^2: 0%−49%) in all subgroups, indicating relative consistency across studies.

4. DISCUSSION

By combining the results from eight prospective observational cohort studies with 3,297 participants, this meta-analysis presents evidence that symptoms of depression are associated with a 57% higher risk of adverse clinical outcome and a 43% higher risk of mortality in patients undergoing PCI. Sensitivity and subgroup analyses suggested that this relationship was not markedly affected by the timing of depression assessment, length of patient follow-up, or type of outcome. Ultimately, the results of this study emphasize the growing recognition that depression is a major risk factor for poor outcomes in coronary heart disease (CHD) patients.

The relationship between CHD and depression has been widely examined. Meta-analyses have demonstrated that depressive symptoms have an unfavorable impact on mortality and cardiovascular events in CHD or post-MI patients[26, 27]. However, few reviews have been conducted on the impact of depression on prognosis in PCI patients. We found that patients with depression exhibited a significantly increased risk for the primary endpoint of MACE and for the secondary endpoint of death. The results of this meta-analysis are in concordance with prior findingsfocusing on other CHD populations.

Considering that several previous studies failed to demonstrate a negative impact of depression on outcome during long-term follow-up[8, 9], we conducted a subgroup analysis according to follow-up time. The predictive value of depression was significant in both groups but less pronounced in the long-time follow-up group (RR = 1.38 vs. RR = 2.09 for short-term follow-up). Whether depression still has a marked effect on the long-term prognosis of PCI requires further study.

Although the prevalence of depression after PCI is approximately 20%−30%, the symptoms are likely to abate during recovery. Previous studies have found that PCI contributes to a higher risk of developing depressive symptoms in CHD patients during hospitalization[28, 29]. Therefore, depression measured too close to the point of interventional treatment may reflect a transient stress response and (or) worsening of physical symptoms. A meta-analysis by Ravven et al[30] showed that the risk of depression decreased throughout the long-term post-CABG period and that measurements taken in the two weeks after the operation may reflect the known consequences of surgery rather than a mood disorder. For these reasons, we also performed a sub-analysis to determine the potential impact of evaluation time on the relationship between depression and prognosis. In this case, depression increased the risk of poor outcome whether assessed during hospitalization (RR = 1.71 [1.06−2.73]) or > 2 weeks after PCI (RR = 1.65 [1.30−2.08]), indicating that the evaluation time has little influence on the adverse effects of depression. This result is in line with another recent finding that depression diagnosis at any time following CAD diagnosis was associated with an increased risk of death[31]. The timing of depression measures and the clinical significance of tests conducted at different times before or after PCI should be carefully considered in future studies.

The results of this meta-analysis have some limitations. Few studies have examined the relationship between depression and adverse clinical outcomes following PCI; thus, only eight studies were suitable for inclusion. Studies included in the

meta-analysis were observational and were subject to patient selection bias, lack of independent events adjudication, and heterogeneity in exposure definitions. Depression was analyzed as a dichotomous variable, limiting examination of relationships between depressive symptom severity and clinical outcomes in patients treated by PCI. In addition, although some studies investigated the prognostic value of depression in different indication groups (SA and ACS), most did not report the results separately; therefore, we were unable to analyze depression risk by patient indications for PCI. Finally, further subgroup analyses were not possible due to the limited number of studies.

5. CONCLUSIONS

This meta-analysis suggests that depression is associated with increased mortality and a greater risk of adverse clinical outcome after PCI. The risk appears to be stable whether depressive symptoms are measured in hospital or following treatment. The identification of depression in PCI patients is critical in view of its negative effect on postoperative recovery, morbidity, and mortality.

CONTRIBUTORS

All authors contributed to conception and design or analysis and interpretation of data. Wen Yi Zhang and Nan Nan performed the experiments. Jin Fan Tian and Xian Tao Song analyzed the data. Xian Tao Song , Wen Yi Zhang, Nan Nan, Jin Fan Tian helped to draft the manuscript or to revise it critically for important intellectual content.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

DATA SHARING STATEMENT

No additional data are available.

PATIENT CONSENT

Consent is not required when conducting a systematic review.

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FIGURE LEGEND

Table 1: Characteristics of studies included in the meta-analysis

Table 2: Sensitivity Analyses: results when given named study is omitted

Box 1: Search strategy in PubMed

Figure 1: PRISMA flow-chart for systematic review of depression and cardiovascular events following PCI

Figure 2: Forest plot of depression and a composite outcome following PCI

Figure 3: Forest plot of depression and all-cause mortality as an outcome following PCI

Figure 4: Funnel plot of depression and a composite outcome following PCI

Figure 5: The influence of different evaluation time of depression on the risk of adverse cardiac events

Figure 6: Relationship between depression and short-term or long-term prognosis after PCI

Box 1: Search strategy in PubMed

#1	depression [Mesh]
#2	depression*[Title/Abstract]
#3	depressive disorder*[Title/Abstract]
#4	depressive mood*[Title/Abstract]
#5	dysthymia [Title/Abstract]
#6	#1 OR #2 O #3 OR #4 OR #5
#7	percutaneous coronary intervention [Mesh]
#8	percutaneous coronary intervention*[Title/Abstract]
#9	PCI [Title/Abstract]
#10	Coronary Balloon Angioplasty [Title/Abstract]
#11	angioplasty [Title/Abstract]
#12	#7 OR #8 OR #9 OR #10 OR #11
#13	#6 AND #12

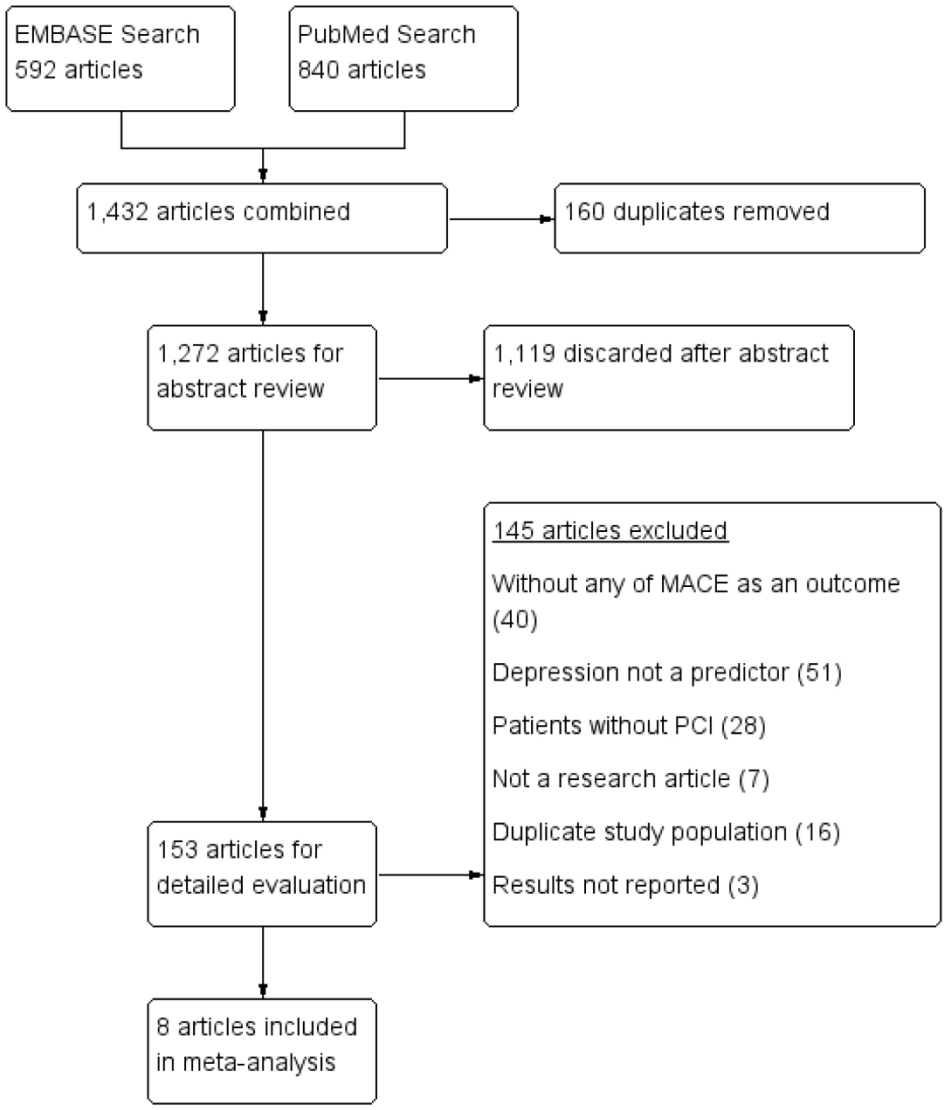
Table 1 : Characteristics of studies included in the meta-analysis

Study	Ethnic	CAD type	Assessment Timing	Measurement Depression	Number of patients (depressed/non-depres)	Outcome	Number of Events (depressed/non-depress	Follow-up Time, year	NOS
Tom A.J.de Jager 2018	Netherlands	SA and ACS	1 month post PCI	HADS	528(104/424)	All-cause mortality	35/98	10	9
Zhi Jian Wang 2013	China	SA and ACS	2 weeks post PCI	HADS MINI	400(154/246)	MACE(all-cause mortality, nonfatal MI and repeat revascularization)	42/32	3	9
Hye Yon Yu 2015	Korea	CAD	Baseline during hospitalisation One month after discharge	PHQ-9	211(64/157)	MACE(rehospitalisati re infarction, revascularisation or cardiac death)	13/21 11/23	1	7
Jin-Hee Park 2015	Korea	CAD	1-4 days post PCI	HADS	133(44/89)	Recurrent Cardiac Events(MI, ISR , revascularization)	11/7	1	6
Milan R van Dijk 2015	Netherlands	SA and ACS	6 months post PCI	HADS	1112(276/836)	All-cause mortality	122/262	10	9
Márcia M.Schmid 2011	Brazil	SA and ACS	Baseline	BDI	125(31/94)	MACE(death, MI or TVR)	6/13	1	7
Thomas Meyer 2014	Germany	stable coronary heart disease	Before PCI	HADS	470(101/369)	All-cause mortality MACE(NR)	11/33 16/57	2 and 5	9
Li Xi ming 2012	China	CAD	Baseline during hospitalisation	SDS	308(112/196)	MACE(all-cause mortality, nonfatal MI and revascularizatio	9/4	1	7

Abbreviations: SA=stable angina; CAD=coronary artery disease; ACS= acute coronary syndrome: PCI=percutaneous coronary intervention; MI=myocardial infarction; MACE=major adverse cardiac events (The definitions differ according to the study and have been shown in the table); TVR=target vessel revascularisation; ISR=in-stent restenosis; HADS=Hospital Anxiety and Depression Scale; MINI= Mini-International Neuropsychiatric Interview; PHQ-9=Patient Health Questionnaire-9; BDI= Beck Depression Inventory; SDS= Self-Rating Depression Scale; NR=information not reported

Table 2: Sensitivity Analyses: results when given named study is omitted

Study Omitted	Lower CI Limit	Risk Ratio	Upper CI Limit	Heterogeneity(I^2)
Li Xi ming 2015	1.26	1.51	1.81	25%
Jin Hee Park 2015	1.25	1.50	1.79	24%
Marcia M.Schmidt 2011	1.27	1.59	1.99	44%
Hye Yon Yu 2015	1.26	1.59	2.00	45%
Thomas Meyer 2014	1.34	1.64	2.02	31%
Zhi Jian Wang 2013	1.21	1.47	1.79	24%
Tom A.J. 2018	1.25	1.63	2.13	44%
Milan R van Dijk 2015	1.26	1.67	2.21	38%



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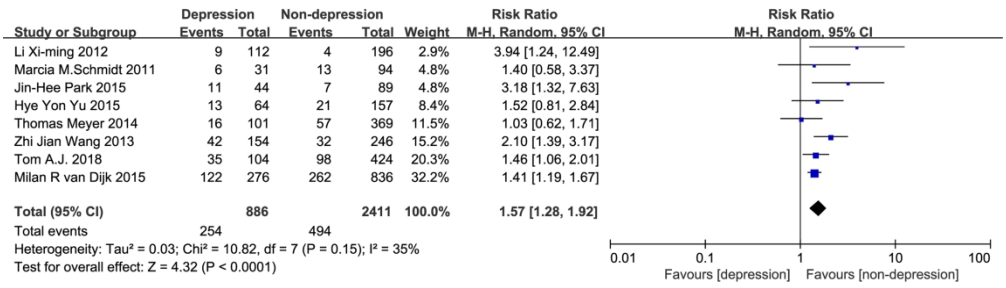

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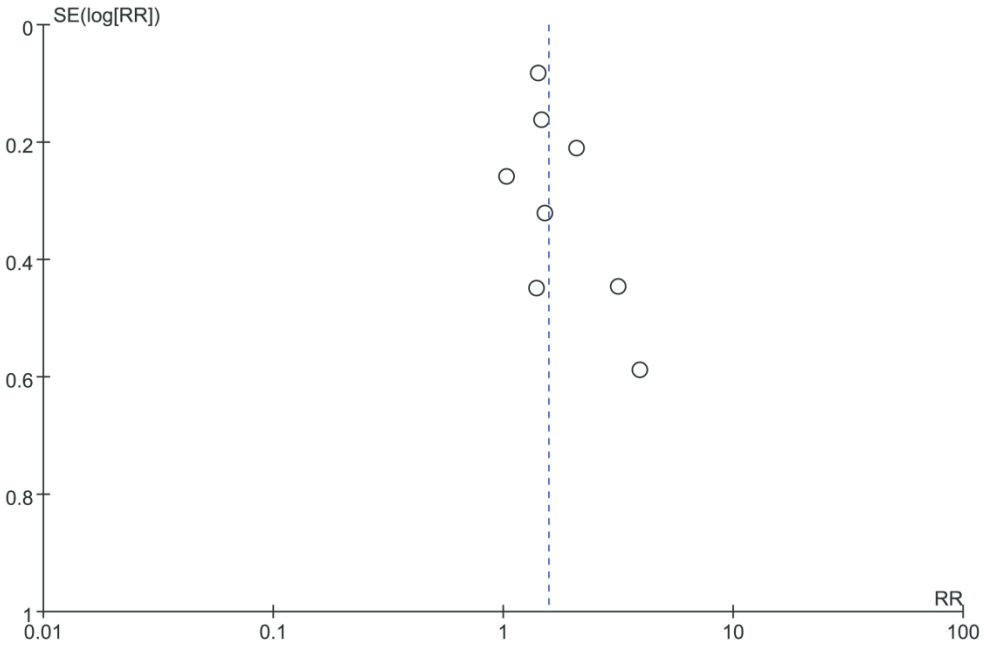

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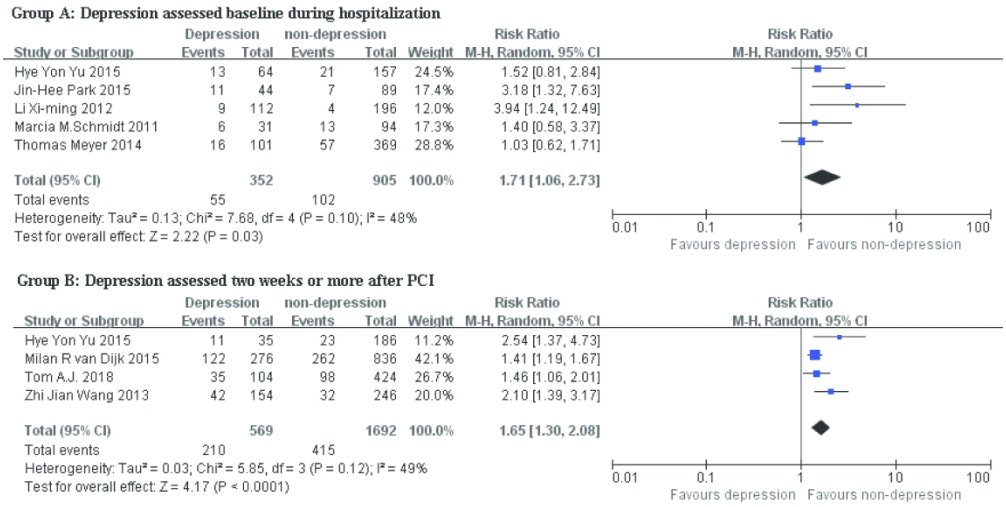

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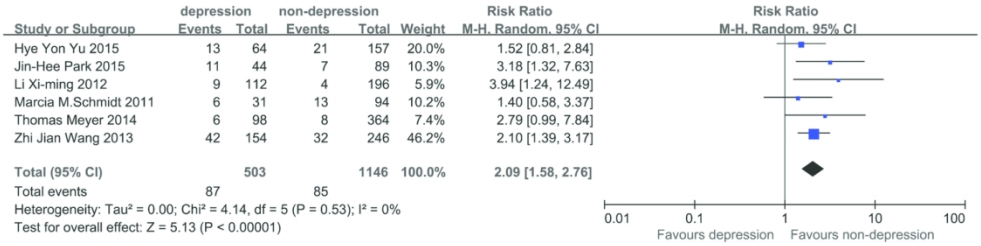
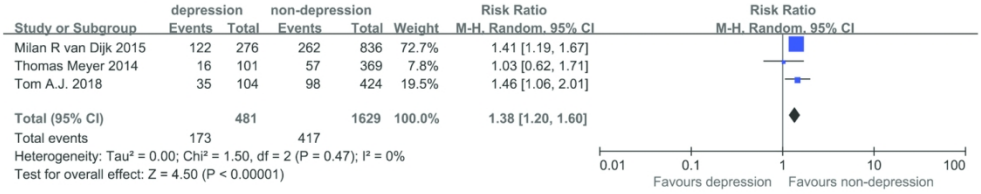
Group A: Forest plot of studies with average follow-up period less than or equal to 3 years



Group B: Forest plot of studies with average follow-up time more than 3 years



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1.Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1.Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2.Methods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2.1 Search strategy and selection criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2.1 Search strategy and selection criteria
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2.1 Search strategy and selection criteria, Box 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2.1 Search strategy and selection criteria
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2.2 Selection and Exclusion Criteria

PRISMA 2009 Checklist

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2.3 Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2.7 Publication bias
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2.5 Data synthesis and statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2.6 Heterogeneity Analysis, Table 1

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2.6 Heterogeneity Analysis 2.7 Publication bias
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2.8 Sensitivity analysis and subgroup analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.1 Study selection and description, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3.1 Study selection and description, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3.4 Publication bias, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Fig. 2, Fig. 3, Fig. 5, Fig. 6
Synthesis of results	21	Present results of all investigations of consistency.	3.2 Meta-analysis

PRISMA 2009 Checklist

			results, Table 1, Fig. 2, Fig. 3, Fig. 5, Fig. 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3.3 Sensitivity analysis 3.4 Publication bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3.3 Sensitivity analysis 3.5 Subgroup analysis Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	4.Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	4.Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5.Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgments

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Impact of Depression on Clinical Outcomes Following Percutaneous Coronary Intervention - A systematic review and meta-analysis

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Impact of Depression on Clinical Outcomes Following Percutaneous Coronary Intervention - A systematic review and meta-analysis

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Impact of Depression on Clinical Outcomes Following Percutaneous Coronary Intervention - A systematic review and meta-analysis

ABSTRACT

Objectives The objective of this meta-analysis was to assess whether depression in PCI patients is associated with higher risk of adverse outcomes.

Design Systematic review and meta-analysis.

Methods EMBASE, PubMed, CINAHL and PsycINFO were searched as data sources. We selected prospective cohort studies evaluating the relationship between depression and any adverse medical outcome, including all-cause mortality, cardiac mortality, and non-fatal events, from inception to February 28, 2019. Two reviewers independently extracted information and calculated the risk of cardiovascular events in patients with preoperative or postoperative depression compared to non-depressed patients.

Results Eight studies (N=3,297) met our inclusion criteria. Most studies found a positive association between depression and adverse cardiovascular outcomes. Meta-analysis yielded an aggregate risk ratio of 1.57 (95% confidence interval 1.28 – 1.92, P<0.0001) for the magnitude of the relation between depression and adverse outcomes.

Conclusions: Our systematic review and meta-analysis suggests that depression is associated with an increased risk of worse clinical outcome or mortality in patients undergoing PCI. Assessment time and length of follow-up do not have a significant effect on this conclusion.

Keywords: depression; percutaneous coronary intervention; prognosis; meta-analysis

Strengths and limitations of this study

1. This study emphasizes the growing recognition that depression is a major risk factor of cardiovascular disease.
2. Depression needs to be fully considered when assessing the prognosis of PCI patients.
3. The quality of the included studies was relatively high.
4. Further analyses were difficult to conduct due to the limited number of studies.

1. INTRODUCTION

Depression and coronary artery disease are highly comorbid conditions with estimates of comorbidity from 20% to 50%[1-3]. Patients with a combination of depression and CAD are at increased risk for negative cardiac outcomes. Prior meta-analyses have demonstrated that depression is associated with a 2−4-fold increase in the risk of future major adverse cardiovascular events in post-myocardial infarction (MI) patients, and this relationship has remained stable despite improvements in diagnosis and treatment[4, 5]. The adverse effects of depression are also observed in patients admitted with unstable angina[6].

Percutaneous coronary intervention (PCI) has become a common revascularization procedure with demonstrated safety and efficacy. Successful PCI significantly reduces the rate of death or revascularization, and improves quality of life[7, 8]. Nonetheless, major adverse cardiac events (MACEs), such as mortality, nonfatal myocardial infarction and repeat PCI, still remain problems. According to several studies, about one-fifth of patients experience depression before PCI, an even greater proportion of patients are depressed after the procedure[9-11]. Besides well-known factors, psychological factors such as depression have been demonstrated to predict adverse cardiac events post-PCI by multiple studies[12-15]. However, not all the studies have suggested that depression was associated with poor prognosis following PCI[16, 17]. Meyer et al.[16] reported depressive symptoms were linked to mortality during two years follow up, but the relationship disappeared three years later. Moreover, de Jager[17] and colleges found the predictive value of depression differ between angina pectoris (SA) and acute coronary syndrome (ACS) cohorts. Furthermore, levels of depression tend to change over time and questions remain about when to assess depression. Considering these problems, we performed a systematic review and meta-analysis to determine the prospective relationship between depression and adverse clinical outcomes after PCI.

2. METHODS

A systematic review and meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]and an a priori study protocol.

2.1 Search strategy and selection criteria

Two authors (Wen Yi Zhang and Nan Nan) independently searched the literature in EMBASE, PubMed, CINAHL and PsycINFO databases without language restriction from inception to February 28, 2019. The search strategy contained keywords related to the population of interest (CAD patients receiving PCI) and keywords related to depression. In PubMed, we used the combination of Medical Subject Headings (MeSH-terms) and relevant free-text terms to identify keywords for each topic. The set operator AND was utilized to form a complementary search strategy (See Box 1).

The search terms from PubMed were adapted to the corresponding vocabulary of EMBASE, CINAHL and PsycINFO databases.

2.2 Selection and Exclusion Criteria

Studies investigating the association between depression and prognosis in patients receiving PCI were retrieved for review. Inclusion criteria were as follows: (1) prospective design, (2) patients diagnosed with CAD and receiving coronary stent implantation, (3) using established assessment instruments or structured clinical interviews to define major depression or depressive symptoms, and (4) reporting an endpoint of all-cause mortality, cardiac mortality, re-hospitalization, or major adverse cardiac events (MACEs).

The exclusion criteria were as follows: (1) case report, animal research, review article or expert opinion, (2) depression not considered as a predictor, (3) unrelated to the search terms, (4) participants without PCI, and (5) data were not reported. For multiple publications from the same cohort[12, 19-22] , we chose the latest or most complete study for assessment[12].

2.3 Data extraction

Two authors independently (Jin Fan Tian and Xue Yao Yang) read the abstract and title of every record identified by the search. Potentially eligible studies were reviewed in detail. Differences in opinion were resolved by consensus. Given that a variety of factors may influence outcome, the following data were extracted from the final eight studies by use of separate spreadsheets: first author's name, study design, ethnicity of the study population, diagnosis of CAD, depression measurement, timing of assessment, outcome definition, length of follow-up, sample size, and number of patients in the depressed and non-depressed groups.

2.4 Quality assessment

We used the Newcastle-Ottawa Scale[23] for quality assessment of included studies. The Newcastle-Ottawa Scale grades three domains: the selection of participants, comparability of the groups, and assessment of outcome[23]. A study can be awarded a maximum of 9 stars for quality. Each study was assessed independently by two investigators. The results are reported in Table 1 and Supplementary Table S1.

2.5 Data synthesis and statistical analysis

Review Manager (RevMan) (Version 5.3, The Cochrane Collaboration, 2014) served as the statistical platform for data management and statistical analyses. Dichotomous frequency data were extracted from each study. Risk ratios (RRs) were calculated from pooled data comparing depressed and non-depressed groups for the likelihood of adverse cardiovascular events. We calculated a pooled RR and 95% confidence interval (95%CI) in the random effects model to account for possible methodological and clinical heterogeneity.

2.6 Heterogeneity Analysis

The statistical heterogeneity among studies was evaluated using the Cochran's Q test, I^2 statistic, and degrees of freedom. The Q test was used to estimate test heterogeneity among trials. The Q value can be used to derive the I^2 value, which is the proportion (%) of variance in a pooled effect size due to heterogeneity rather than chance. Based on I^2, heterogeneity was rated as low (I^2<50%), moderate (50%−75%), or high (>75%) [24].

2.7 Publication bias

Publication bias was assessed by means of Egger's regression asymmetry test[25] and Begg's test[26]. We used the funnel plot to examine whether sample sizes influenced the results of the meta-analysis.

2.8 Sensitivity analysis and subgroup analysis

To further explore the sources of heterogeneity, we conducted a sensitivity analysis by omitting one study at a time and calculating the pooled effect size, 95%CI, and heterogeneity of the remaining studies (Table 2).

We conducted subgroup analyses to assess possible moderator effects for the association of depression with prognosis after PCI. These moderator effects included the time point for evaluating depression, the type of outcome, and length of follow-up.

2.9 Patients and public involvement statement

No patients were involved in the design, recruitment or conduct of the study. There are no plans to disseminate the results of the research to the patient community included in the trials of the review.

3. RESULTS

3.1 Study selection and description

A flow diagram of the literature search is illustrated in Figure 1. A total of 2,000 records were identified through the literature search, with 1,826 articles remaining when duplicates were removed. These articles were evaluated in detail. Ultimately, eight studies met the inclusion criteria and were included in the meta-analysis[10-17]. The included studies were published between 2011 and 2018, and had follow-up periods ranging from 1 year to 10 years. Sample size ranged from 125 to 1,112, and the eight studies included a total of 3,297 participants from the Netherlands, China, Korea, Brazil, and Germany. The quality of the studies was good, with four of eight studies (50%) rated 9 stars on the Newcastle-Ottawa Scale.

Of the identified studies five measured depression only once, varying from before the procedure during hospitalization to six months post PCI. Three of the studies assessed depression twice. The research by Yu et al. (2017) measured depression at baseline during hospitalization and one month after discharge. Wang et al. (2013) and Li et al. (2012) assessed depression both before and after the PCI. These two studies suggested depression was present in nearly 40% of the postoperative patients, increasing more than 10 percentage points than that before the operation.

Four of the eight studies defined depression according to the Hospital Anxiety and

Depression Scale (HADS) [27]. The level of depression was considered clinically relevant at a cut-off HADS score of 8. Wang et al. (2013) used a combination of HADS and the Mini-International Neuropsychiatric Interview (MINI) to identify patients with depression. Yu et al. (2017) used the 9-question Primary Care Evaluation of Mental Disorders brief patient health questionnaire (PHQ-9) to define depression (non-depressed ≤ 4, depressed 5−27). Schmidt et al. (2011) identified patients with depression using the Beck Depression Inventory (BDI) with 20 points as the cutoff value. The study by Li et al. (2012) defined depression according to the Zung Self-Rating Depression Scale (Zung SDS).

Two studies reported all-cause mortality, four studies reported adverse cardiac events as an outcome, and two studies reported both all-cause mortality and adverse cardiac events separately. MACE was defined according to the individual study criteria and included all-cause mortality, nonfatal MI, revascularization (as evidenced by repeated PCI, target vessel revascularization [TVR], target lesion revascularization [TLR], or coronary artery bypass graft [CABG]), and re-hospitalization with cardiac death. Specific characteristics of the included studies are summarized in Table 1.

3.2 Meta-analysis results

3.2.1 Effect of depression assessed at any time on composite outcome

For the pooled sample (eight studies), depression assessed at any time period resulted in a significant increase in the incidence of cardiac events (risk ratio = 1.57, [95%CI] 1.28–1.92) in the random effects model, indicating that depressed individuals have a 57% greater risk of poor outcome than non-depressed patients. The overall results are displayed in Figure 2.

3.2.2 Depression and all-cause mortality as an outcome

As shown in Figure 3, in the sub-analysis of four studies that included all-cause mortality as an outcome, depression was associated with a significantly higher risk of death after PCI (RR = 1.43 [1.24−1.65]).

3.3 Sensitivity analysis

To determine the reliability of the results, sensitivity analyses were performed by omitting one study at a time. No individual study had a substantial impact on the pooled effect size and heterogeneity. The RR changed slightly only when excluding the study by Dijk et al. (2016)[12] with the largest number of participants (RR = 1.67 [1.26−2.21]) (see Table 2).

3.4 Publication bias

The funnel plot demonstrated slight asymmetry (Figure 4), suggesting that there may be unpublished studies which have found no relationship between depression and clinical outcomes. However, neither Egger's test nor Begg's test revealed evidence of publication bias ($p > 0.1$), although these results should be interpreted with caution due to the limited number of included studies.

3.5 Subgroup analysis

3.5.1 Subgroup analysis by depression assessment time

The pooled RR was also calculated for studies assessing depression during hospitalization and for those measuring depression 2 weeks or more after PCI. For studies with depression assessed in hospital, the RR = 1.71 [1.06−2.73] and for those with depression evaluated 2 weeks or more post-PCI, the RR = 1.65 [1.30−2.08] (Figure 5).

3.5.2 Subgroup analysis by follow-up time

We used 1 year as the cut-off for distinguishing short- from long-term follow-up to evaluate whether the prognostic value of depression for predicting adverse outcomes was temporally limited. The pooled RR for studies with follow-up time less than or equal to 1 year was 2.04 [1.27−3.28], whereas the increase in risk became less pronounced when examining composite outcomes with longer follow-up times (RR = 1.46 [1.19−1.80]) (Figure 6).

3.6 Heterogeneity

Heterogeneity across studies was determined to test the appropriateness of combining studies. Slight heterogeneity was apparent among all included studies (I^2=35%, p for heterogeneity = 0.15). However, heterogeneity remained low (I^2: 0%−49%) in all subgroups, indicating relative consistency across studies.

4. DISCUSSION

By combining the results from eight prospective observational cohort studies with 3,297 participants, this meta-analysis presents evidence that symptoms of depression are associated with a 57% higher risk of adverse clinical outcome and a 43% higher risk of mortality in patients undergoing PCI. Sensitivity and subgroup analyses suggested that this relationship was not markedly affected by the timing of depression assessment, length of patient follow-up, or type of outcome. Ultimately, the results of this study emphasize the growing recognition that depression is a major risk factor for poor outcomes in coronary heart disease (CHD) patients.

The relationship between CHD and depression has been widely examined. Meta-analyses have demonstrated that depressive symptoms have an unfavorable impact on mortality and cardiovascular events in CHD or post-MI patients[5, 28]. However, little is known about the impact of depression on prognosis in PCI patients. We found that patients with depression exhibited a significantly increased risk for the primary endpoint of MACE and for the secondary endpoint of death. The results of this meta-analysis are in concordance with prior findings focusing on other CHD populations.

While a positive correlation between depression symptoms and adverse cardiac outcomes was found in our research, careful consideration should be given to different methods of depression assessment. In the majority of included articles, depression was defined based on scores of a self-report screening instrument, for example, the Hospital Anxiety and Depression Scale (HADS), rather than structured or semi structured diagnostic interviews. Although several screening instruments have been showed high sensitivity or specificity for CAD patients and were used more

often by physicians in general hospitals to assess depression[29-31], no consensus has yet been reached on the optimal screening tool for use in identifying depression in patients with coronary heart disease[32]. Since the word 'depression' may include different meanings ranging from transient negative emotions through to serious clinical symptoms, more cautious needs to be taken when investigating the prognostic value of depression in further studies.

Considering that several previous studies failed to demonstrate a negative impact of depression on outcome during long-term follow-up[16, 17], we conducted a subgroup analysis according to follow-up time. The predictive value of depression was significant in both groups but less pronounced in the long-time follow-up group (RR = 1.46 vs. RR = 2.04 for short-term follow-up). Whether depression still has a marked effect on the long-term prognosis of PCI requires further study.

Although the prevalence of depression after PCI is approximately 20%−30%, the symptoms are likely to abate during recovery. Previous studies have found that PCI contributes to a higher risk of developing depressive symptoms in CHD patients during hospitalization[9, 33]. Therefore, depression measured too close to the point of interventional treatment may reflect a transient stress response and (or) worsening of physical symptoms. A meta-analysis by Ravven et al[34] showed that the risk of depression decreased throughout the long-term post-CABG period and that measurements taken in the two weeks after the operation may reflect the known consequences of surgery rather than a mood disorder. For these reasons, we also performed a sub-analysis to determine the potential impact of evaluation time on the relationship between depression and prognosis. In this case, depression increased the risk of poor outcome whether assessed during hospitalization (RR = 1.71 [1.06−2.73]) or > 2 weeks after PCI (RR = 1.65 [1.30−2.08]), indicating that the evaluation time has little influence on the adverse effects of depression. This result is in line with another recent finding that depression diagnosis at any time following CAD diagnosis was associated with an increased risk of death[35]. The timing of depression measures and the clinical significance of tests conducted at different times before or after PCI should be carefully considered in future studies.

The results of this meta-analysis have some limitations. Few studies have examined the relationship between depression and adverse clinical outcomes following PCI; thus, only eight studies were suitable for inclusion. Studies included in the meta-analysis were observational and were subject to patient selection bias, lack of independent events adjudication, and heterogeneity in exposure definitions. Depression was analyzed as a dichotomous variable, limiting examination of relationships between depressive symptom severity and clinical outcomes in patients treated by PCI. In addition, although some studies investigated the prognostic value of depression in different indication groups (SA and ACS), most did not report the results separately; therefore, we were unable to analyze depression risk by patient indications for PCI. Finally, because of the small number of studies in this field, we could not conduct further subgroup analyses, and this may have certain impact on the accuracy of our research.

5. CONCLUSIONS

This meta-analysis suggests that depression is associated with increased mortality and a greater risk of adverse clinical outcome after PCI. The risk appears to be stable whether depressive symptoms are measured in hospital or following treatment. The identification of depression in PCI patients is critical in view of its negative effect on postoperative recovery, morbidity, and mortality.

CONTRIBUTORS

All authors contributed to conception and design or analysis and interpretation of data. Wen Yi Zhang and Nan Nan performed the experiments. Xian Tao Song, Jin Fan Tian, and Xue Yao Yang analyzed the data. Wen Yi Zhang, Nan Nan and Jin Fan Tian drafted the manuscript. Xian Tao Song and Xue Yao Yang helped to revise it critically for important intellectual content.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

DATA SHARING STATEMENT

No additional data are available.

PATIENT CONSENT

Consent is not required when conducting a systematic review.

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2017;3(4):296-302.

FIGURE LEGEND

Box 1: Search strategy in PubMed

Table 1: Characteristics of studies included in the meta-analysis

Table 2: Sensitivity Analyses: results when given named study is omitted

Supplementary Table S1: Quality assessment of each study included in the meta-analysis, based on the Newcastle-Ottawa Scale (NOS)

Figure 1: PRISMA flow-chart for systematic review of depression and cardiovascular events following PCI

Figure 2: Forest plot of depression and a composite outcome following PCI

Figure 3: Forest plot of depression and all-cause mortality as an outcome following PCI

Figure 4: Funnel plot of depression and a composite outcome following PCI

Figure 5: The influence of different evaluation time of depression on the risk of adverse cardiac events

Figure 6: Relationship between depression and short-term or long-term prognosis after PCI

Box 1: Search strategy in PubMed

#1	depression [Mesh]
#2	depression*[Title/Abstract]
#3	depressive disorder*[Title/Abstract]
#4	depressive mood*[Title/Abstract]
#5	dysthymia [Title/Abstract]
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	percutaneous coronary interventions [Mesh]
#8	percutaneous coronary intervention*[Title/Abstract]
#9	PCI [Title/Abstract]
#10	Coronary Balloon Angioplasty [Title/Abstract]
#11	angioplasty [Title/Abstract]
#12	#7 OR #8 OR #9 OR #10 OR #11
#13	#6 AND #12

Table 1 : Characteristics of studies included in the meta-analysis

Study	Ethnic	CAD type	Assessment Timing	Measurement o Depression	Number of patient (depressed/non-depressed)	Outcome	Number of Events (depressed/ non-depressed)	Follow-up Time, year	NOS
De Jager et al. 2018[17]	Netherlands	SA and ACS	1 month post PCI	HADS	528(104/424)	All-cause mortality	3/98	10	9
Wang et al. 2013[11]	China	SA and ACS	2 weeks post PCI	HADS MINI	400(154/246)	MACE(all-cause mortality, nonfatal MI, and revascularization)	7/32	3	9
Yu et al.2015[13]	Korea	CAD	Baseline during hospitalization One month after discharge	PHQ-9	211(64/157)	MACE(re-hospitalizatic re infarction, revascularization or cardiac death)	7/21 7/23	1	7
Park et al. 2015[15]	Korea	CAD	1-4 days post PCI	HADS	133(44/89)	Recurrent Cardiac Events(MI, ISR , revascularization)	7/7	1	6
Dijk et al. 2015[12]	Netherlands	SA and ACS	6 months post PCI	HADS	1112(276/836)	All-cause mortality	12/262	10	9
Schmidt et al. 2011[14]	Brazil	SA and ACS	Baseline	BDI	125(31/94)	MACE(death, MI or TVR)	6/13	1	7
Meyer et al. 2014[16]	Germany	stable coronary heart disease	Before PCI	HADS	470(101/369)	All-cause mortality MACE(NR)	11/33 15/57	2 and 5	9
Li et al. 2012[10]	China	CAD	Baseline during hospitalization	SDS	308(112/196)	MACE(all-cause mortality, nonfatal MI a revascularization)	8/4	1	7

Abbreviations: SA=stable angina; CAD=coronary artery disease; ACS= acute coronary syndrome: PCI=percutaneous coronary intervention; MI=myocardial infarction; MACE=major adverse cardiac events (The definitions differ according to the study and have been shown in the table); TVR=target vessel revascularization; ISR=in-stent restenosis; HADS=Hospital Anxiety and Depression Scale; MINI= Mini-International Neuropsychiatric Interview; PHQ-9=Patient Health Questionnaire-9; BDI= Beck Depression Inventory; SDS= Self-Rating Depression Scale; NOS= Newcastle-Ottawa Scale; NR=information not reported

Table 2: Sensitivity Analyses: results when given named study is omitted

Study Omitted	Risk Ratio, 95% CI	Heterogeneity (I^2)	P value
De Jager et al. 2018[17]	1.63 (1.25, 2.13)	44%	P<0.001
Wang et al. 2013[11]	1.47 (1.21, 1.79)	24%	P<0.001
Yu et al. 2015[13]	1.59 (1.26, 2.00)	45%	P<0.001
Park et al. 2015[15]	1.50 (1.25, 1.79)	24%	P<0.001
Dijk et al. 2015[12]	1.67 (1.26, 2.21)	38%	P<0.001
Schmidt et al. 2011[14]	1.59 (1.27, 1.99)	44%	P<0.001
Meyer et al. 2014[16]	1.64 (1.34, 2.02)	31%	P<0.001
Li et al. 2012[10]	1.51 (1.26, 1.81)	25%	P<0.001

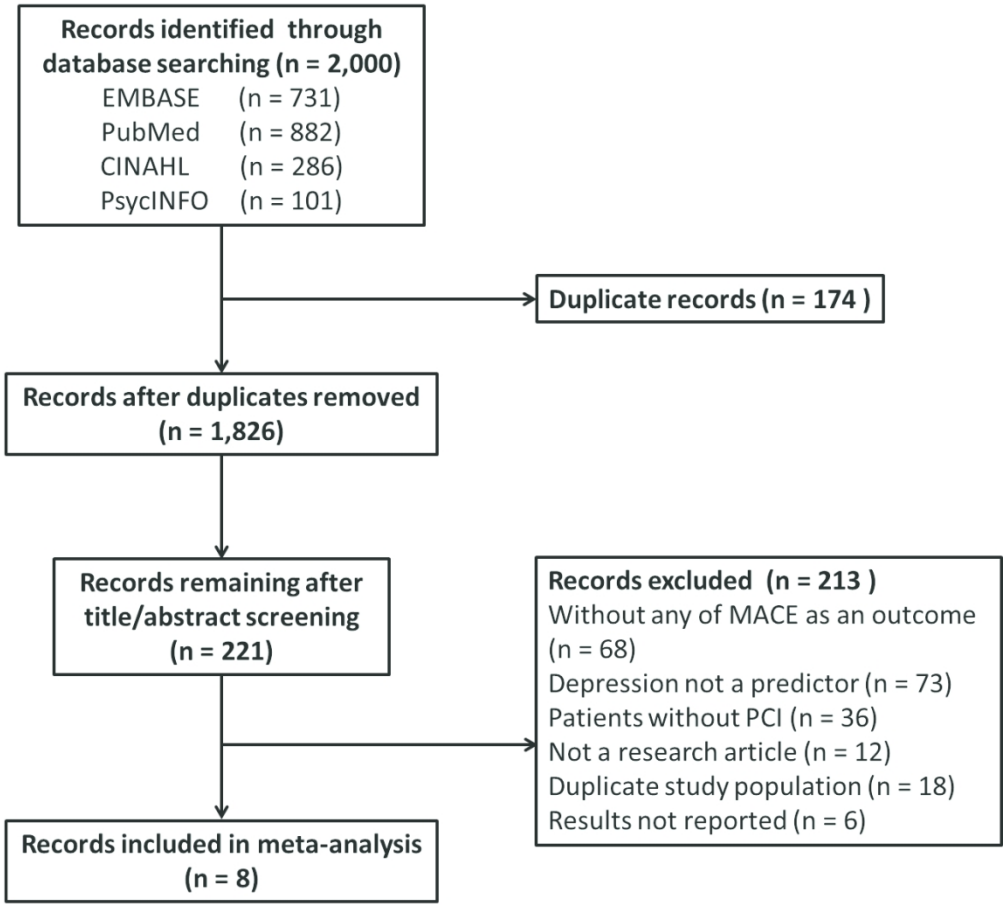

Figure 1: PRISMA flow-chart for systematic review of depression and cardiovascular events following PCI

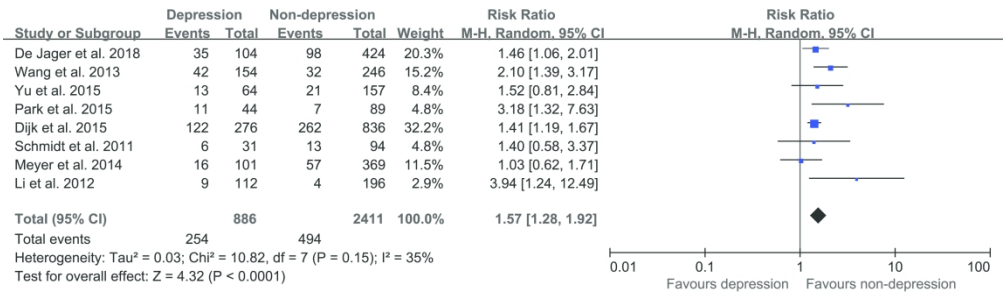

Figure 2: Forest plot of depression and a composite outcome following PCI

Figure 3: Forest plot of depression and all-cause mortality as an outcome following PCI

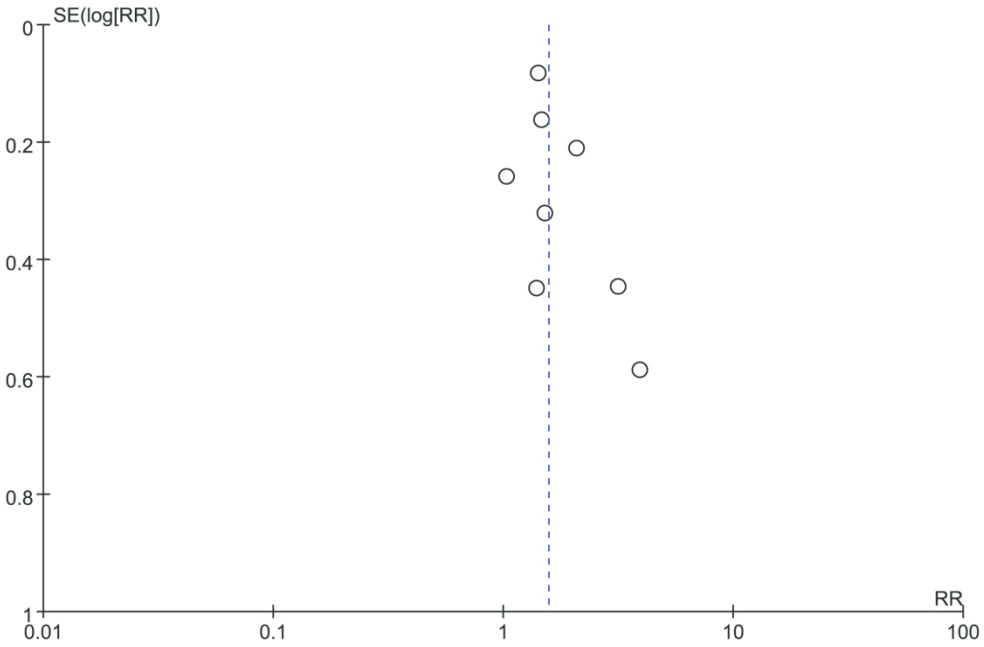

Figure 4: Funnel plot of depression and a composite outcome following PCI

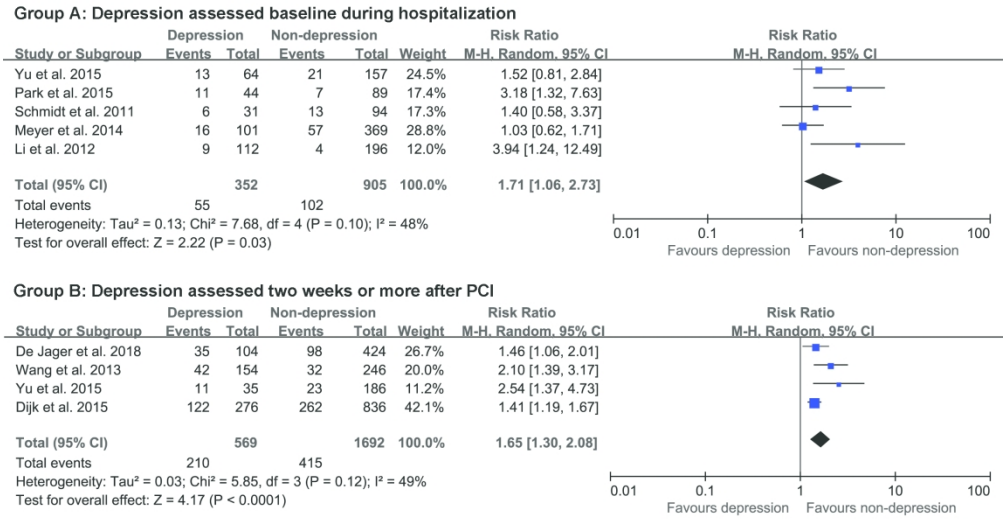

Figure 5: The influence of different evaluation time of depression on the risk of adverse cardiac events

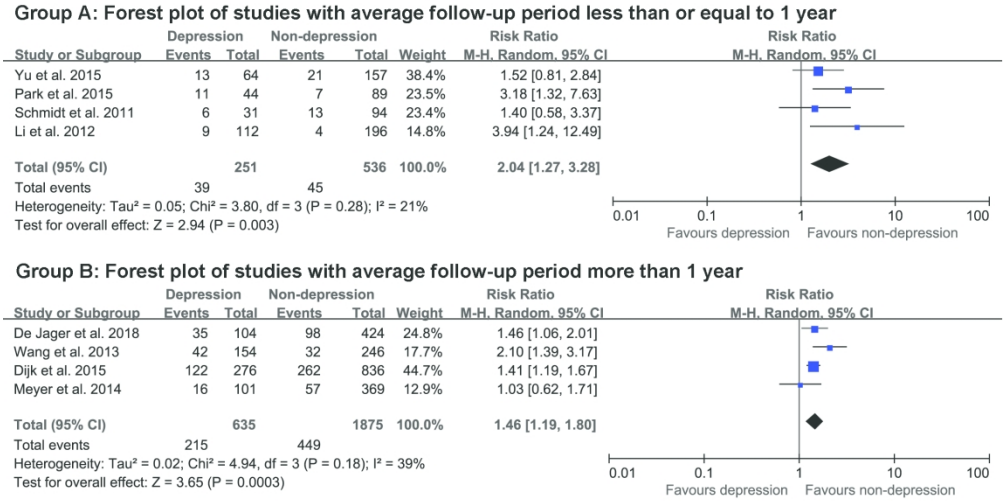

Figure 6: Relationship between depression and short-term or long-term prognosis after PCI

Supplementary Table S1: Quality assessment of each study included in the meta-analysis, based on the Newcastle-Ottawa Scale (NOS) [a]

	SELECTION			COMPARABILITY		OUTCOME			Total score
Study ID	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	
De Jager et al. 2018[17]	★	★	★	★	★★	★	★	★	9
Wang et al. 2013[11]	★	★	★	★	★★	★	★	★	9
Yu et al. 2015[13]	★	★	★	★	N/R	★	★	★	7
Park et al. 2015[15]		★	★	★	N/R	★	★	★	6
Dijk et al. 2015[12]	★	★	★	★	★★	★	★	★	9
Schmidt et al. 2011[14]	★	★	★	★	N/R	★	★	★	7
Meyer et al. 2014[16]	★	★	★	★	★★	★	★	★	9
Li et al. 2012[10]	★	★	★		★ for age	★	★	★	7

[a] A maximum of one star for each item within the 'Selection' and 'Outcome' categories; A maximum of two stars for 'Comparability' category. For 'Comparability', one star was awarded if the study controlled for age, another star was awarded if the study controlled for important CHD risk factors; N/R, not reported.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1.Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1.Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2.Methods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2.1 Search strategy and selection criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2.1 Search strategy and selection criteria
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2.1 Search strategy and selection criteria, Box 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2.1 Search strategy and selection criteria
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2.2 Selection and Exclusion Criteria

PRISMA 2009 Checklist

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2.3 Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2.7 Publication bias
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2.5 Data synthesis and statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2.6 Heterogeneity Analysis, Table 1

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2.6 Heterogeneity Analysis 2.7 Publication bias
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2.8 Sensitivity analysis and subgroup analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.1 Study selection and description, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3.1 Study selection and description, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3.4 Publication bias, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Fig. 2, Fig. 3, Fig. 5, Fig. 6
Synthesis of results	21	Present results of all investigations of consistency.	3.2 Meta-analysis

PRISMA 2009 Checklist

			results, Table 1, Fig. 2, Fig. 3, Fig. 5, Fig. 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3.3 Sensitivity analysis 3.4 Publication bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3.3 Sensitivity analysis 3.5 Subgroup analysis Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	4.Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	4.Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5.Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgments

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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