The Effect of Single Nucleotide Polymorphisms on Depression in Combination With Coronary Diseases: Protocol for a Systematic Review and Meta-analysis

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Protocol

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Abstract

Background: Depression and coronary heart disease (CHD) have common risk mechanisms. Common single nucleotide polymorphisms (SNPs) may be associated with the risk of depression combined with coronary heart disease.

Methods: This protocol was designed according to the PRISMA-P guidelines. CENTRAL in the Cochrane Library, MEDLINE Ovid, Embase Ovid, Web of Science, CNKI, CQVIP, SinoMed, Wanfang Data, and ChiCTR will be systematically searched. We will include case-control studies and cohort studies investigating the relationship between gene SNPs and depression and coronary heart disease comorbidities. The Newcastle-Ottawa Scale (NOS) will be used to assess the risk of bias. When measuring dichotomous outcomes, we will use the risk ratio (RR) and 95% confidence interval (95%CIs) in a cohort study and use the odds ratio (OR) and 95% confidence interval (95%CIs) in a case-control study. Five genetic models (allele model, homozygous model, heterozygous model, dominant model, and recessive model) will be evaluated for each included study. Subgroup analysis by ethnicity will be performed. If necessary, post hoc analysis will be made according to different types.

Discussion: The purpose of this meta-analysis is to comprehensively study the current evidence and assess the association between single nucleotide polymorphisms and susceptibility of depression in combination with coronary heart disease.

Systematic review registration: This protocol was prospectively registered in the PROSPERO (registration number CRD42021229371).

1. Introduction

Depression is a common mental disorder. According to WHO reports, more than 264 million people suffer from depression in global terms[1]. Depression and coronary heart disease (CHD) are leading causes of disability and disease burden in high-income countries[2]. So far, many meta-analyses and reviews have proved that depression has a strong correlation with the increase in the incidence and mortality of CHD[3–9]. The World Mental Health Survey results showed that cardiac patients have twice the risk of depression than those without heart disease[10]. In 2006, Thombs et al.[11] found the probability of patients with myocardial infarction suffering from depression is between 15.5% and 31.1%. In 2007, Egede et al.[12] found the prevalence of major depressive disorder(MDD) in cardiac patients is 9.3%, while it is 4.8% in no comorbidity individual. Depression can adversely affect the prognosis of CHD patients[13]. Depressed patients are challenging to comply with medical treatment[14]. Ziegelstein et al.[15] raised that depressed myocardial infarction patients should follow recommendations to reduce heart risk difficultly during the recovery period. Lichtman et al.[16] proved that high levels of biomarkers predicting cardiac events or promoting atherosclerosis are found frequently in people with depression.

CHD and mental diseases' common risk mechanisms include endothelial cell and platelet dysfunction, inflammation, autonomic dysfunction, and hypothalamus-pituitary-adrenal cortex (HPA) axis

dysfunction[17]. Researchers put forward the concept of "gene overlap" based on these common risk mechanisms, meaning involvement of the same genes in the pathogenesis of both CHD and depression[18].

5-HT transporter(5-HTT) is encoded by the SLC6A4 gene localized in chromosome 17q11.1-q12[19] and expressed in brain and blood cells. The pathophysiological mechanism of depression may be associated with an imbalance of 5-HT uptake in the synaptic cleft mediated by 5-HT transporter[20, 21]. Besides, alterations of 5-HT mechanisms may be related to developing an enhanced cardiovascular risk[22, 23]. Galan et al.[24] showed that 5-HT is an agonist of platelets in peripheral tissues. It enhances the procoagulant response and increases thrombogenesis on damaged vascular surfaces. Some meta-analyses and prospective studies have concluded that 5-HT transporter linked promoter region (5-HTTLPR) polymorphisms may significantly impact the risk of depression in CHD patients[25–29]. Phillips et al.[30] found that patients with depression who carry the L allele in patients after coronary artery bypass graft surgery in the United States were more likely to have adverse events; Nakatani et al.[31] showed that the risk of depression and cardiac adverse events in patients with acute myocardial infarction in Japan during the recovery period is related to the S allele; Kim et al.[32] proposed that Koreans carrying the S allele are related to the occurrence of post-acute coronary syndrome (ACS) depression; A prospective study by Warnke et al.[28] on Germans found that 5-HTTLPR rs25531 A/G may be an important marker for detecting people at risk of late-onset depression in CHD patients.

Dysfunctional serotonin 2A receptor (5-HT2AR) and serotonin 2C receptor (5-HT2CR) are implicated in neuropsychiatric disorders[33]. As one of the main pharmacological therapeutic targets for MDD, 5-HT2AR has a high affinity for antidepressants[34]. The 5-HT2CR antagonist is a commonly used drug for the treatment of significant depression[35]. In a case-control study conducted in Russia by Golimbet et al.[36], which included 169 male CHD patients (135 of whom had depression), they found that 5-HTR2A polymorphism − 1438A/G is related to the severity of depressive symptoms in CHD patients, and the risk of moderate and severe depression in patients with allele G is 2.4 times higher than that in patients with genotype AA. The 5-HTR2C polymorphism Cys23Ser is associated with depression, and Ser alleles have a higher incidence in CHD patients[36].

Apelin (APLN), an endogenous neuropeptide, is the cognate ligand for the G protein-coupled receptor APJ (putative receptor protein related to angiotensin II receptor type-1, AT1R)[37]. Apelin/APJ system plays a potential role in emotional behavior[38]. However, the role of apelin in depression is controversial[39]. In the cardiovascular system apelin-APLNR pathway plays a central role, and circulating apelin is a promising CHD predictor[40]. Wang et al.[41] conducted a case-control study of 269 patients with CHD (122 of them suffering from depression) and 184 healthy people in China. It is the first report that after adjusting drinking habits, insomnia, hypertension, and stroke history, patients with CHD who carry the APLNR rs9943582 C allele still have a higher risk of depression.

Brain-derived neurotrophic factor (BDNF) promotes survival, differentiation, and maintenance of neurons in the peripheral and nervous system. It regulates vascular development and response to injury by

activating local TrkB-expressing endothelial cells(ECs) and inducing mobilization and recruitment of myeloid cells' subpopulation [42]. Lower BDNF levels are associated with the persistence of depressive symptoms in CHD patients[43]. The Val66Met polymorphism of the BDNF gene is associated with depression[44]. Kang et al.[45] found that Korean ACS patients carrying the BDNF Met allele were related to the prevalence and persistence of depression. Bozzini et al.[25] found that the BDNF AA genotype is involved in the pathogenesis of CHD in women and the susceptibility of CHD related to depression in a case-control study involving 99 CHD patients and 143 healthy people in Italy. Liu et al.[46] found a significant correlation between CHD with depression and the SNP rs6265 located in the fourth exon of the BDNF gene and a potential correlation with the promoter region rs13306221.

Apolipoprotein E (ApoE) participates in plasma lipoprotein metabolism by interacting with cell surface receptors[47]. ApoE prevents atherosclerosis progression[48], and lack of ApoE leads to spontaneous development of atherosclerosis[49]. Studies in the population show that ApoE polymorphism is the primary determinant of an individual's susceptibility to CHD[50]. ApoE is also involved in the process of nervous system growth and regeneration after injury[47]. Ji et al.[51] included a case-control study of 30 CHD patients, 26 CHD patients with depression and, 30 healthy people in China, which showed that the ApoEε4 allele might play an important role in depression in combination with CHD.

FK-506 binding protein 51 (FKBP5) is a co-chaperone of heat shock protein 90 (hsp90). A complex of Hsp90 and FKBP51 slows down glucocorticoid receptor (GR) transport into the nucleus and reduces GR's activity[52], which leads to the weakening of GR's negative feedback on the HPA axis. HPA axis is the central stress hormone system and is linked with the development of CHD and depression when exposed to stressors[53, 54]. FKBP5 might confer a shared genetic risk for both CHD and depression[55]. Brandt et al.[55] included a prospective study of 268 German CHD patients and found that depression was only associated with the FKBP5 rs1360780 C allele in patients with previous myocardial infarction or coronary artery reconstruction. Wang et al.[56] included a case-control study of 271 CHD patients (123 of them with depression) and 113 healthy controls from the Han nationality in northern China. They found that rs9470079 may be a potential gene locus of co-morbidity of CHD and depression.

Glucocorticoid receptor (GR) is a steroid hormone receptor, which belongs to the nuclear receptor superfamily of transcription factors[57]. It is highly expressed in the HPA axis's critical regions, including the hippocampus, amygdala, and hypothalamus[58]. As a negative feedback mechanism of the HPA axis, GR in the hypothalamus and pituitary gland binds to cortisol, inhibits ACTH and CRH's secretion, and regulates the homeostasis of the HPA axis[59]. More and more studies have verified that GR dysfunction is involved in the pathological mechanism of depression and depressive behavior caused by stress[60–62]. Over the past few decades, many researchers have confirmed a causal relationship between glucocorticoid receptor gene (Nuclear receptor subfamily 3 group C member1, NR3C1) SNPs depression[63–65]. Currently, the relationship between glucocorticoids and atherosclerosis is complicated and unclear. A review pointed out that GR's chronic excessive activation induces cardiovascular risk factors, such as obesity, insulin resistance, glucose, intolerance, dyslipidemia, and hypertension[66]. NR3C1 polymorphism may affect the sensitivity of cells to glucocorticoid by changing the transcription

level of NR3C1, affecting the number of receptors or affinity of hormones and receptors, thus leading to individual dependence or resistance to glucocorticoid[67]. Otte et al.[68] tested four NR3C1 gene polymorphism types (ER22/23EK, BclI C/G, n363, and 9beta A/G) in a cross-sectional genetic association study of 526 white American patients with chronic CHD. The study results indicate that haplotype 3, which contains the minor allele of the 9beta A/G polymorphism, has a gene dose-dependent relationship with depression. Haplotype 3 may be a susceptibility factor for depression in CHD patients.

Serum/glucocorticoid-regulated kinase 1 (SGK1) is a serine/threonine kinase, a member of the AGK Kinase family, and contributes to transport regulation hormone release, neuron excitability, inflammation, cell proliferation, and apoptosis[69]. SGK1 participates in renal Na^+ excretion by aldosterone, insulin, and insulin-like growth factor 1(IGF1)[70, 71], thereby affecting blood pressure. The genetic variance of SGK1 is pertinent to blood pressure[72]. SGK1, significantly associated with depression, is a mediator for cortisol effects on neurogenesis and GR function[73]. Considering the complicated relationship among SGK1, CHD, and depression, it is reasonable to propose that SGK1 may be a co-pathogenic gene in the comorbid mechanism of CHD and depression. Han et al.[74] tested the SGK1 gene in 257 Han Chinese CHD patients (69 cases of depression) and 107 healthy people. They found that both rs1743963 GG genotype and rs1763509 AA genotype were associated with an increased risk of depression in CHD patients. Haplotype GGA significantly increases the risk of depression in CHD patients, and haplotype AAG may be a protective factor for patients with CHD and depression.

Plasminogen activator inhibitor-1 (PAI-1) is a principal regulatory protein in the fibrinolytic system, as the primary inhibitor of tissue plasminogen activator (tPA) and urokinase plasminogen activators (uPA)[75]. Decreased fibrinolytic activity in CHD patients is associated with PAI-1[76]. Plasminogen activator inhibitor-1 gene (*SERPINE1*) is located on chromosome 7 (7q22.1). Evidence suggests that *SERPINE1* genetic variants may play a role in MDD and CHD susceptibility[75, 77]. In a study covering 42 depressed patients, 65 CHD patients, and 132 healthy people in China, Lin et al.[78] found that the frequency of PAI-1 gene − 675 locus 4G/4G gene and 4G allele in depressed patients and CHD patients are higher than the healthy control group. There is no significant difference between the 4G/4G genotype frequency and the 4G allele frequency. Therefore, PAI-1 gene 4G may be a comorbid gene of CHD and depression. Xia et al.[79] included 75 CHD patients with depression, 91 CHD patients, 56 patients with depression, and 63 healthy people. The study found that the PAI-1 gene 4G/4G and 4G allele frequency in CHD patients and CHD with depression significantly higher than that of the other two groups. It also shows that the co-morbidity of CHD and depression is related to the coexistence of the 5-HTTLPR gene SS genotype and PAI-1 gene 4G/4G genotype.

However, the association between gene polymorphisms and depression in combination with CHD is controversial. Up till now, a high-quality, comprehensive systematic review of possible gene SNPs on depression in combination with CHD has not been conducted or published. This study will systematically review the correlation between depression in combination with CHD and SNPs using meta-analysis.

2. Methods

This protocol was performed complying with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and published on the International Prospective Register of Systematic Reviews(PROSPERO) on 10 January 2021. It will last update on 20 April 2021 (registration number CRD42021229371)[80].

2.1. Literature Search

2.1.1 Information sources

We will search Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE Ovid, Embase Ovid, Science Citation Index Expanded (Web of Science), and also search for the China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), China Biomedical Literature Service System (SinoMed) and Wanfang Data. To ensure literature saturation, We will search the Chinese Clinical Trial Registry (ChiCTR) for ongoing or unpublished studies and search in Human Genomic Epidemiology Navigator(HuGENavigator) based on the genes retrieved from the above database. We manually searched reference lists of systematic reviews and meta-analyses on this topic and retrieved studies.

2.1.2 Search strategy

We will use medical subject headings (MeSH) to develop literature search strategies.

We searched MEDLINE Ovid up to 10 January 2021 for phrases:

#1 (polymorphism or mutation or variant).sh. [sh = MeSH subject heading]

#2 (polymorphism or mutation or variant).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

#3 depression.sh.

#4 (depression or depressive).mp.

#5 coronary disease.sh.

#6 ((heart disease or cardiovascular disease or coronary artery disease or coronary atherosclerosis or angina pectoris or pectoris or acute coronary syndrome or myocardial infarction or myocardial ischemia or ischemic heart disease or CHD or CAD or CVD or ACS or MI).mp.

#7 1 or 2

#8 3 or 4

#9 5 or 6

#10 7 and 8 and 9

The search strategy will be schematically illustrated using the PRISMA search flow diagram (see Fig. 1).

2.2. Inclusion Criteria

2.2.1 Participants

We will include studies with case group participants diagnosed as depression combined with CHD and the control group participants diagnosed as CHD or diagnosed as depression or dinary people, as defined by the trialists or according to guidelines. This study's CHD includes angina, acute coronary syndrome, ischemic heart disease, and myocardial infarction — no requirement on age and gender.

2.2.2 Exposure

Any SNPs that can be retrieved are associated with depression combined with coronary diseases. Candidate genes include the gene encoding 5-HTT, 5-HT2AR, 5-HT2CR, APLN, BDNF, ApoE, FKBP5, GR, SGK1, PAI-1, and so on. We will not restrict the retrieved genotypes or polymorphic mutation types.

2.2.3 Comparator

The polymorphic mutation types of the genotypes in the case group.

2.2.4 Outcome

The proportion of participants with depression combined with coronary diseases.

2.2.5 Types of study to be included

We will include case-control studies and cohort studies investigating the relationship between gene SNPs and depression and CHD comorbidities. The blinding, language, year, publication format, and publication status will be irrespective.

2.3. Exclusion criteria

We will use freely available online translators to translate eligible studies in any other language into English. If a translation of the article is unclear, we will contact the original authors by email. If no response is obtained after one month, we will exclude the article. We only include peer-review studies published in scientific journals. Master’s theses, dissertations, abstracts from conference proceedings, technical reports, articles with missing data, and papers where no full text will be excluded.

2.4. Data Extraction

Review authors worked in pairs independently screened titles and abstracts to identify potential eligible trials, extracted data using an electronic data collection form created in Microsoft Excel. We resolved any disagreements through discussion, or we asked a third author who does not involve in the data extraction process. Review authors worked in pairs independently extracted the following information: publication data (i.e., year, country, authors); study characteristics and design; characteristics of trial participants; trial diagnostic criteria; the prevalence of SNPs associated with depression combined with coronary disease (mutations detected—original amino acid, mutated amino acid, position, number of carriers of mutated allele in case group and control group, and number of non-carriers of mutated allele in both) among study population were recorded, whether the genotype frequencies conformed to Hardy-Weinberg Equilibrium (HWE), number of dropouts and final number of participants used in the analyses.

2.5. Quality Assessment

Review authors working in pairs assessed the risk of bias in the included trials. According to the Newcastle-Ottawa Scale (NOS), we will assess the risk of bias about the following items: selection, comparability, and exposure.

2.6. Statistical Analysis

We will make five comparisons for each polymorphism: 1) allele model (B vs. A), 2) homozygous model (BB vs. AA), 3) heterozygous model (AB vs. AA), 4) dominant model (BB + AB vs. AA), 5) recessive model (BB vs. AA + AB). We assessed our intervention effects with both fixed-effect model and random-effects model meta-analyses. We reported both results when results differed (e.g., one giving a significant intervention effect, the other no significant intervention effect). We put greater weight on the estimate closest to the zero effect (the highest P-value). We assessed the outcome with a P-value of 0.05 or less as statistically significant. We will use the risk ratio (RR) for measuring dichotomous outcomes with 95% confidence intervals (CIs) for head-to-head comparison meta-analysis for a cohort study. We will use the odds ratio (OR) for measuring dichotomous outcomes with 95% confidence intervals (CIs) for head-to-head comparison meta-analysis for a case-control study.

In cases of available data, we will plan to perform the subgroup analyses by ethnicity. If necessary, post hoc analysis will be made according to different types, including angina, acute coronary syndrome, ischemic heart disease, and myocardial infarction. We planned to perform sensitivity analyses by omitting single studies from each meta-analysis to assess these studies' effect on the pooled effect size in the overall model and the subgroup analyses. A study will be omitted if it differed from the other studies based on the pre-specified potentially confounding variables (age, education, ethnicity, history of mental illness). These factors may impact outcomes.

3. Discussion

This article is the first meta-analysis of all currently known candidate genes for depression in combination with CHD. Many clinical studies have shown that genetic information can help to predict the development of diseases, select the most effective therapeutic interventions, and reduce

complications[81]. Exploring the comorbid genes of CHD and depression can help clinicians choose the best treatment drugs and other therapies for patients, reduce the economic burden and time cost of patients, and avoid medical waste at the same time. This research also inspires the development of new drugs. If the data is of poor quality, partial results may be obtained, and future research suggestions will be provided. If the diagnostic criteria are different or participants of different races in the same area, the results may be biased.

Abbreviations

CHD: Coronary heart disease; HPA: hypothalamus–pituitary– adrenocortical; 5-HTT: 5-HT transporter; 5-HT: serotonergic; 5-HTTLPR: 5-HT transporter linked promoter region; 5-HT2AR: Serotonin 2A receptor; 5-HT2CR: serotonin 2C receptor; GPCR: G-protein-coupled receptor; MDD: Major depressive disorder; APLN: Apelin; BDNF: Brain-derived neurotrophic factor; ECs: endothelial cells; ApoE: Apolipoprotein E; FKBP5: FK-506 binding protein 51; hsp90: heat shock protein 90; GR: glucocorticoid receptor; NR3C1: Nuclear receptor subfamily 3 group C member1; SGK1: Serum/glucocorticoid-regulated kinase 1; IGF1: insulin-like growth factor 1; PAI-1: Plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; uPA: urokinase plasminogen activators; SERPINE1: plasminogen activator inhibitor-1 gene; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; PROSPERO: published on the International Prospective Register of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CNKI: the China National Knowledge Infrastructure; CQVIP: Chongqing VIP; SinoMed: China Biomedical Literature Service System; ChiCTR: the Chinese Clinical Trial Registry; HuGENavigator: Human Genomic Epidemiology Navigator; MeSH: medical subject headings; SNPs: single nucleotide polymorphisms; CAD: coronary artery disease; CVD: cardio vascular disease; ACS: acute coronary syndrome; MI: myocardial infarction; HWE: Hardy-Weinberg Equilibrium; NOS: the Newcastle-Ottawa Scalel.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

DZK and LG designed the protocol. DZK, YW, and MMW will search all databases, screen and select potential eligible trials. LG, HL, and SCZ will extract and collect data. SCZ, YW, and ZZ will evaluate all studies for the risk of bias. A discussion will resolve any discrepancies between the independent assessments. If consensus cannot be reached, a third member of the research team (GLY or LQH) will be invited to mediate. DZK and LG will undertake the statistical analysis, DZK and LG will write the first draft of the resultant manuscript, with ongoing critical input from other authors. All authors have read and agreed with this protocol. DZK is the guarantor. LG and DZK are co-corresponding authors, and they contributed equally to the article.

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Figures

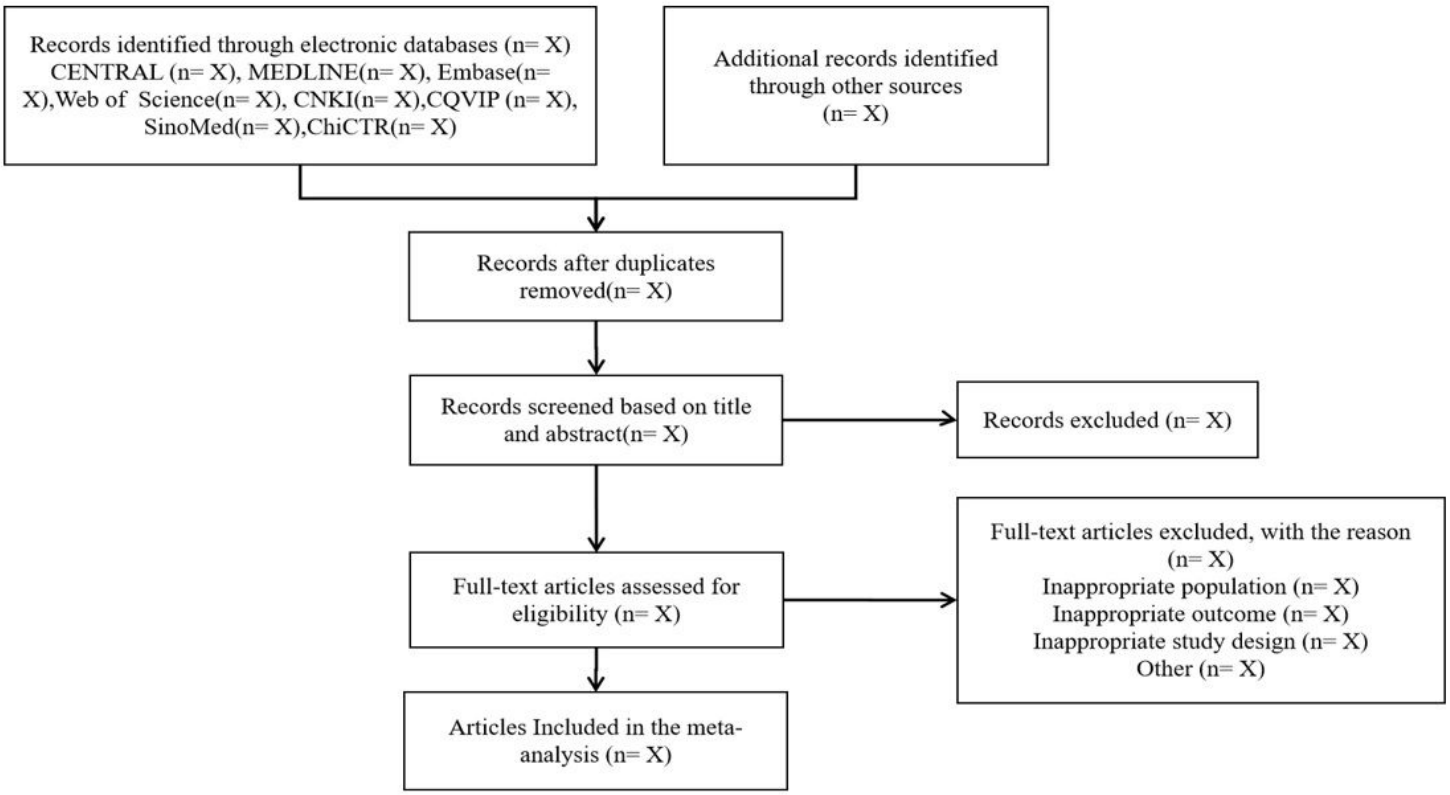

Figure 1

Flow diagram

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