Antidepressant’s long-term effect on cognitive performance and cardiovascular system

التأثير طويل المدى لمضادات الاكتئاب على الأداء الإدراكي والجهاز القلبي الوعائي

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Abstract:

Background: The nature of antidepressants and their adverse effects should be considered when treating severe depression in individuals with psychotic symptoms. Antidepressant prescription rates have risen steadily over the last 30 years, affecting people of all ages.

Aim: The goal of this study was to see if depression and antidepressant usage were linked to long-term changes in cognitive function and cardiovascular health.

Methodology: Meta-analysis was performed using PRISMA guidelines along with using the SPIDER search framework using related keywords on different search engines ie. Google scholars, PubMed, Scopus, ISI, etc. Total (n=2256) papers were obtained and assessed for eligibility. Altogether 15 studies were included using databases and other methods. The Newcastle-Ottawa Scale examined the grades provided by the data after numerous screenings.

Result: A distinct link was found between antidepressants with cognitive performance and the cardiovascular system. Dementia and hypertension were prevailing long-term effects caused by frequent use of antidepressants in chronic and mild depression.

Keywords:

Depression, Depressive Disorder, Antidepressants, Long-term effect, Cognition, Cognitive Performance, Cardiovascular system.

ملخص

الخلفية: ينبغي مراعاة طبيعة مضادات الاكتئاب وآثارها الجانبية عند علاج الاكتئاب الحاد لدى الأفراد الذين يعانون من أعراض ذهانية. وقد ارتفعت معدلات وصف مضادات الاكتئاب بشكل مطرد على مدار الثلاثين عامًا الماضية، مما أثر على الأشخاص من جميع الأعمار.

الهدف: هدفت هذه الدراسة إلى معرفة ما إذا كان الاكتئاب واستخدام مضادات الاكتئاب مرتبطين بتغيرات طويلة المدى في الوظيفة الإدراكية وصحة القلب والأوعية الدموية.

المنهجية: أُجري تحليل تلوي باستخدام إرشاداتPRISMA ، بالإضافة إلى إطار عمل البحث SPIDER، باستخدام كلمات مفتاحية ذات صلة في محركات بحث مختلفة، مثل Google Scholasticsو PubMedو ScopusوISI، وغيرها. تم الحصول على إجمالي (ن = 2256) ورقة بحثية وتقييمها للتحقق من أهليتها. أُدرجت 15 دراسة باستخدام قواعد البيانات وطرق أخرى. فحص مقياس نيوكاسل-أوتاوا الدرجات المقدمة من البيانات بعد العديد من الفحوصات.

النتيجة: وُجدت صلة واضحة بين مضادات الاكتئاب والأداء الإدراكي والجهاز القلبي الوعائي. كان الخرف وارتفاع ضغط الدم من الآثار طويلة المدى السائدة الناتجة عن الاستخدام المتكرر لمضادات الاكتئاب في حالات الاكتئاب المزمن والخفيف.

الكلمات المفتاحية: الاكتئاب، اضطراب الاكتئاب، مضادات الاكتئاب، التأثير طويل المدى، الإدراك، الأداء الإدراكي، الجهاز القلبي الوعائي..

Introduction:

Globally, Depressive disorder has been reported growing increasingly [1] which usually causes impairment and disability [2]. Whatsoever, the treatment of such disorders has resulted in an elevated failure rate with side effects like slow response, and low efficacy [3, 4]. As a result, there is a pressing demand for innovative, safe drugs with significant pharmacological effective-ness. According to the Global Health Data Exchange, depression affects 251-310 million people globally [5]. We can see from the map in fig: 1 that mental illness-es are highly frequent over the world: one out of every seven persons (15%) has one or more mental disorders; similarly, Today, the global prevalence of depression is estimated to be between 2% and 6% of the population. In general, people in their seventies and eighties have a larger risk of developing depression than people in plenty of other age demographics[6].

Furthermore, up to 30% of those affected are thought to be resistant to therapy. Despite the fact that standard therapies have indeed been proven to be effective in older people [7] in practical reality, such regimens are frequently unsatisfactory to patients or are laden with adverse effects [8]. A various number of chronic illnesses including cancer [9], cardiovascular disease [10], stroke [11], Alzheimer's disease [12], Parkinson's disease [13], and other physiological and cognitive impairments, has been related to depressive disease [14] .

Antipsychotics are among the most often prescribed psychiatric narcotics, and their usage bas "skyrocketed in the last two decades throughout the world (15-17). Antidepressants may be neuroprotective owing to the fewer harmful amyloid-ß formation, increased neurotrophic factor, and promotion of neurogenesis, according to several mechanistic investigations [18-20].

Antidepressant drug prescriptions in US NHs have climbed dramatically from 21.9 percent in 1996 to 47.5 percent in 2006 [21].

Some antidepressants, on the other hand, have cardiovascular, adverse effects that may increase rather than decrease the risk of cardiac events. Orthostatic hypotension, delayed cardiac conduction, increased heart rate, and decreased heart rate variability is all possible side effects of tricyclic antidepressants (TCAs). Depression has been demonstrated to respond well to evidence-based psychotherapies such as cognitive-behavioral therapy and interpersonal psychotherapy. [22]. Antidepressant safety in susceptible groups, such as older persons and those with or at risk of cardiovascular disease, is difficult to assess. Many of our current understandings of antidepressant cardio-vascular effects derive from epidemiological studies of antidepressant safety in older persons including those with cardiovascular disease. Several longitudinal studies have found no link between antipsychotic drugs usage and cardiovascular outcomes [23], whereas others have discovered that individuals using anti-depressants may just have a decreased risk of cardiac events. Coupland and colleagues used a large cohort study to evaluate whether or not all of the individuals were depressed [24] No significant links between generic antipsychotic usage and myocardial infarction (MI) were discovered, throughout a 5-year follow-up.

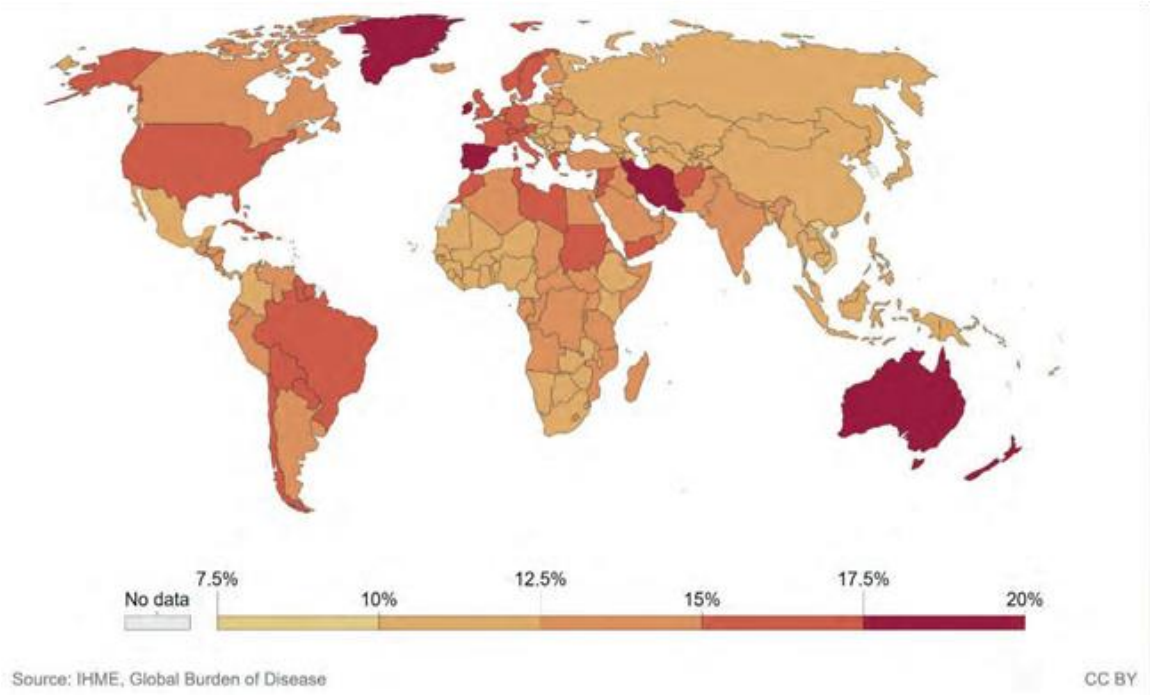

Fig. 1. Share of population with mental disorder (Retrieved from: Institute for Health Metrics and Evaluation, 2019).

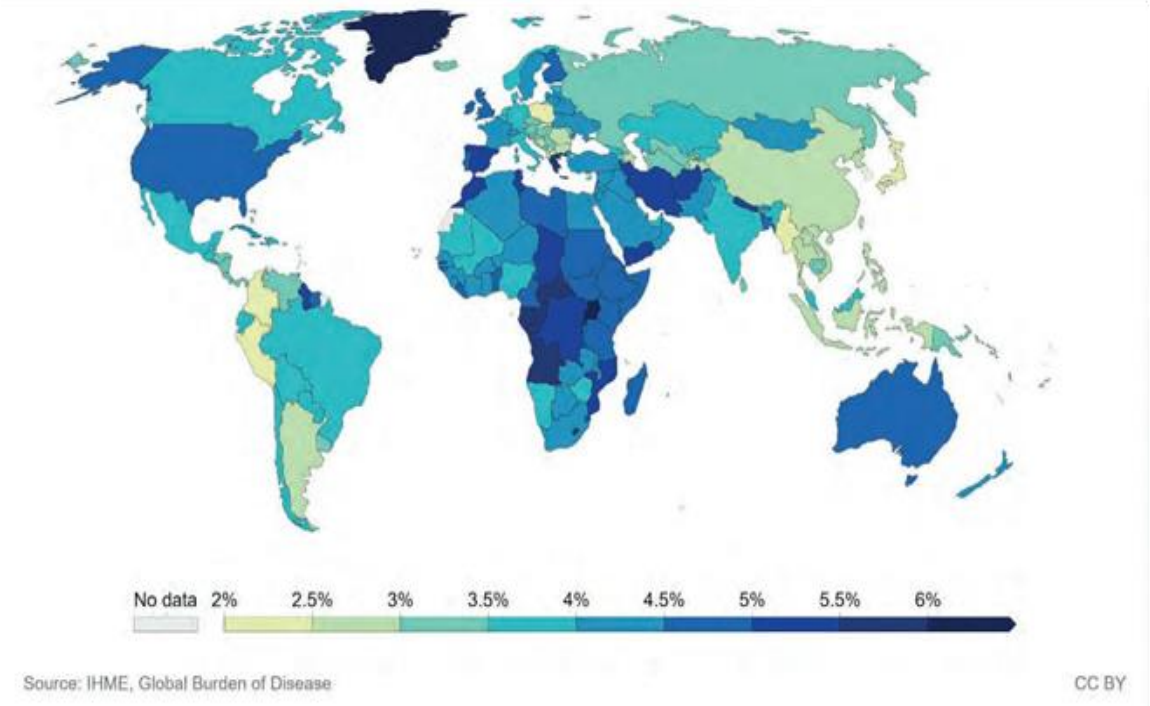

Fig. 2. Share of population with depression (Retrieved from: Institute for Health Metrics and Evaluation, 2019)

The majority of research looking at the impact of antidepressants on cognitive performance have looked at processes including concentration, cognition, dilemma, and visuoperception? The difficulty to concentrate and remember is a common complaint among de-pressed people. In response to these concerns, several researchers have observed depression-related cognitive impairment, as evidenced by poor results on cognitive measures such as alertness and consciousness (25-27) Several investigations on the impact of antidepressant medications on cognitive functioning in healthy subjects have been conducted in recent decades. Several tricyclic antidepressants, including imipramine and amitriptyline, caused substantial cognitive damage in both short and long-term studies [28].

Even after controlling for clinical and biological indicators of heart failure severity, depression has been linked to worse outcomes and increased rates of mortality in various cohorts of patients with heart failure [29-37]. Although remission of depression appears to be linked to increased survival [38], the effects of antidepressant therapy on heart failure outcomes remain unknown. Although the therapeutic significance of these features has yet to be determined, selective serotonin reuptake inhibitors (SSRIs) have been demonstrated to limit platelet activity, enhance endothelium stability, and have anti-inflammatory effects [39].

We therefore conducted this meta-analysis to review the long-term effect and association of after effects of antidepressants on the individual's cognitive performance and cardiovascular performance.

Methodology:

The systematic review was carried out in accordance with the PRISMA checklist and criteria [40]. And framework of SPIDER as a model for developing eligibility for qualitative systematic reviews was followed [41], as seen in Tab. 1

Tab. 1
SPIDER framework for searching strategy

Sample	Depressive patients, antidepressants intake, as well as patients with other psychological and even physiological disorder.
Phenomenon of Interest	Effect of antidepressants on patient's cognition and cardiac condition
Design	Review of already published articles using Search engines.
Evaluation	Effects including long term and short term effect.
Research Type	Quantitative, qualitative, retrospective, longitudinal, cohort, reviews, systematic reviews, meta-analysis, controlled study, case report

Criteria of Literature collection:

This systematic review used search engines like PubMed and Google Scholars. To sort the data, certain filter tools in the search channels are used. We looked at articles that were published within the decade between January 2012 and January 2022. There are several keywords associated with the review i.e. depressive patients, antidepressants, SSRI, anticholinergic, long-term, short-term effect, cognition, cardio-vascular system. Longitudinal, prospective, retrospective, case study, cohort, reviews, meta-analysis, and follow-up were all used in conjunction with the previous terms. Tab. 2 and Appendix 2 list the keywords utilized.

Tab. 2
Keywords used in Search engine to retrieve data.

Search Framework	Keywords used to search
Population	Adults, Teenagers, Depressed people,
Variables	Antidepressant, Depressive disorder, Long-term, Short-term, Antidepressants, Cognition, SSRI, anticholinergic, serotonin, benzodiazepines, fluoxetine, Prozac.
Outcome	learning disabilities, memory, ADHD, Dementia, PTSD, cardiovascular disease

Criteria for Exclusion and Inclusion:

The majority of recent obesity-related research publications were inclusive. High-impact factor journals, were used to gather high-quality research. Articles were to be (1) published in their native language or English, (2) concentrated on the effect of antidepressants on cognition and the cardiovascular system, (3) published in peer-reviewed journals between January 2012 and January 2022, and (4) have a direct and appropriate literature on the research area.

We looked at studies that defined depression and other psychological illnesses using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. We only preserved research that was published in peer-reviewed journals, excluding conference papers and dissertations when data from the same sample was used in several publications.

Data Extraction:

A standardized form was used to capture data on the year of publication, location, setting, and characteristics of research participants (sample size, age, and percentages of men and women), depressive and other psychological disorder disorders with the use of antidepressants. The extraction sheets from each study were examined for consistency, and any inconsistencies were resolved by a conversation with the other researchers.

Quality assessment:

The Newcastle-Ottawa Scale [42] was used to evaluate the research quality. The research groups chosen, the study groups' comparability was determined, and the outcome. We considered the studies to be of high, medium, or poor quality if the evaluations ranged from 7-9, 4-6, and 1-3. The number nine denotes the highest level of methodological competence. Each trial's assessment information can be found in Appendix 3 and Tab.3.

Tab. 3

Studies Description and scorings

Antidepressants	Topic	Author	Description	Quality score
Anticholinergic Drugs	Anticholinergic drugs and risk of dementia: case control study	46	There was a link between anticholinergic medicines and the development of dementia in the future. This might be due to a class specific impact or medications used to treat dementia's early symptoms.	9
SSRIs, fluoxetine	The effect of selective serotonin reuptake inhibitors on cognitive function in patients with Alzheimer's disease and vascular dementia: focusing on fluoxetine with long follow-up periods	48	SSRIs, particularly fluoxetine, have an alleviating influence on cognitive performance.	7
metformin	Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus	49	Metformin's long-term impact on depression cognition in diabetic individuals	9
Not mentioned	Depression as a modifiable factor to decrease the risk of dementia	47	Dementia is more likely to strike older males with a history of depression	8
SSRIs, Paroxetine, zolpidem	A case report on elderly psychotic- like symptoms caused by antidepressant discontinuation	50	Rapid deterioration in work and daily activities, as well as knowledge of sickness and memory and cognitive function loss	8
SSRI, TCA, SNRI, Serotonin modulators	Use of antidepressant medications among older adults in European long-term care facilities: a cross-sectional analysis from the SHELTER study	51	Antidepressants were taken by nearly half of those who experienced depressed symptoms (32%).	8
Not Specific	Depression and Antide-pressants as Potential Risk Factors in Dementia: A Systematic Review and Meta-analysis of 18 Longitudinal Studies	45	Depression is linked to an increased incidence of dementia, and antidepressant treatment has not been proved to be a dementia protective factor.	7
Paroxetine, TSDDs, Serotonin	Cumulative Antidepressant Use and Risk of Dementia in a	44	depression medications used in late life do not appear to be associated with dementia	9

antagonist	Prospective Cohort Study		risk	
BZAs, SSRI, SNRI, NA, AA	PTSD, Psychotropic Medication Use, and the Risk of Dementia Among US Veterans: A Retrospective Cohort Study	43	The use of BZAs or SNRIs at the start of the study was linked to a considerably higher probability of dementia diagnosis, even in the absence of a PTSD diagnosis.	9
Serotonin, nortriptyline, maprotiline and amitriptyline	Effects of Antidepressants on Cognitive Functioning of Elderly Patients	52	It's difficult to draw more strong conclusions from this research because of the methodological variability, particularly the difference in applied neuropsychological tests. More research is required. A common under-standing of a standardized subset of tests would be a huge step forward in allowing future research to be compared.	7
SSRIs	Antidepressant Use and Cognitive Outcomes in Very Old Women	53	linked to a higher chance of cognitive impairment After 5 years, among the oldest elderly ladies,	8
SSRIs, benzodiazepine s	Depression, antidepressants, and long-term mortality in heart failure	54	In HF patients, the use of antidepressants and benzodiazepines is safe in terms of survival.	8
fluoxetine, sertraline and paroxetine, amlodipine, lercanidipine with some of the SSRIs, venlafaxine or bupropion, granulopenia, vortioxetine warfarin,	Adverse effects of interactions between antidepressants and medications used in treatment of cardiovascular disorders	55	Cardiac arrest, Swelling of lower limbs, headaches	9
SSRIs, AAs	Antidepressants and the Risk of Cardiovascular Events in Elderly Affected by Cardiovascular Disease	56	SSRI and AA users have a higher risk of cardiovascular events. Current usage of SSRIs and AAs has been linked to an elevated risk of arrhythmia and stroke.	9
Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	Direct and indirect effects of psychopharmacological treatment on the cardiovascular system	57	Some newer antidepressants have been linked to elevated blood pressure and maybe increased bleeding risks.	8

RESULTS

Study Selection:

(n=2256) papers were obtained from numerous databases, and (n =172) relevant articles were retrieved from various websites, organizations, and pre-existing citations in the databases. The papers were all exported to the citation program Mendeley (Version 1.17.13), with duplicated studies (n=1221; n=64) being eliminated. Abstracts and titles were examined to sort the relevant themes, and complete articles were retrieved and evaluated based on eligibility criteria if the abstract and title offered adequate information. In addition, owing to inaccessibility and eligibility rules, whereas, some were excluded and not recovered. As indicated in the flow diagram Fig: 3, numerous reviews (n=39, 11) were successfully obtained. and a total of (n=13) papers got included within the part of this review, as shown in fig: 4 and 5.

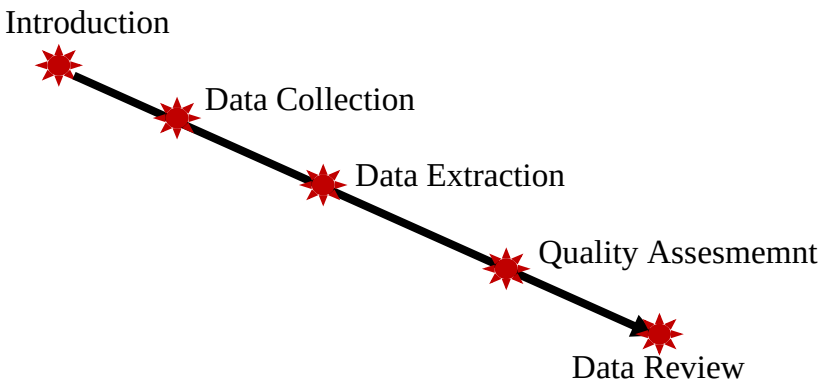

Fig: 3. Flow Diagram of Research Design

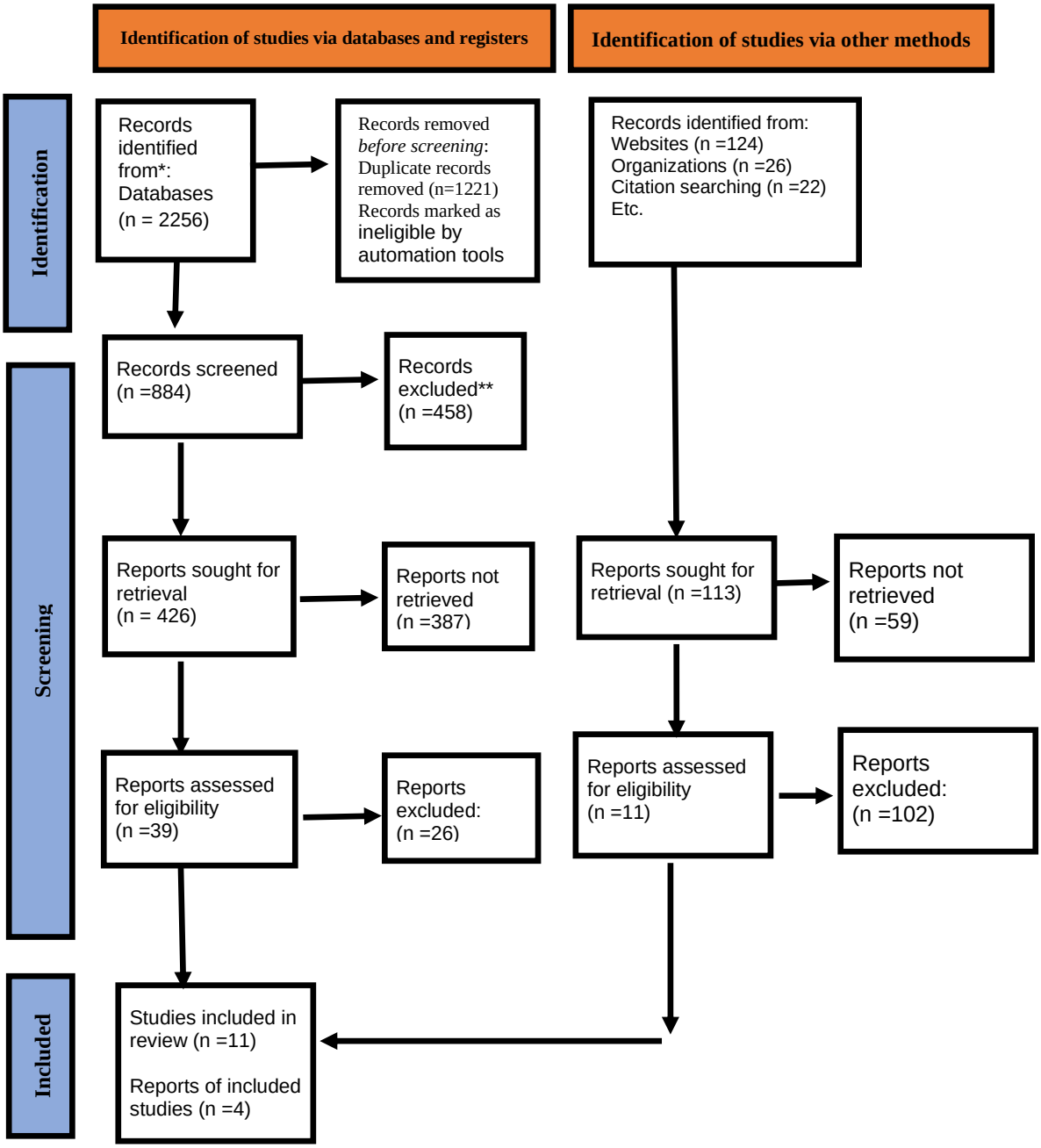

Fig: 4. PRISMA flow diagram of article selection criteria.

Reviewed Studies:

After many evaluations and considerations, 15 papers were chosen to examine the long-term and short-term effects of antidepressants on cognition function and cardiovascular system. Between 2012 and 2021, the research papers were published. The studies examined throughout the

research had participants from regions all over the world. Antidepressants were linked to cognition and the cardiovascular system in every other trial and review included in the analysis.

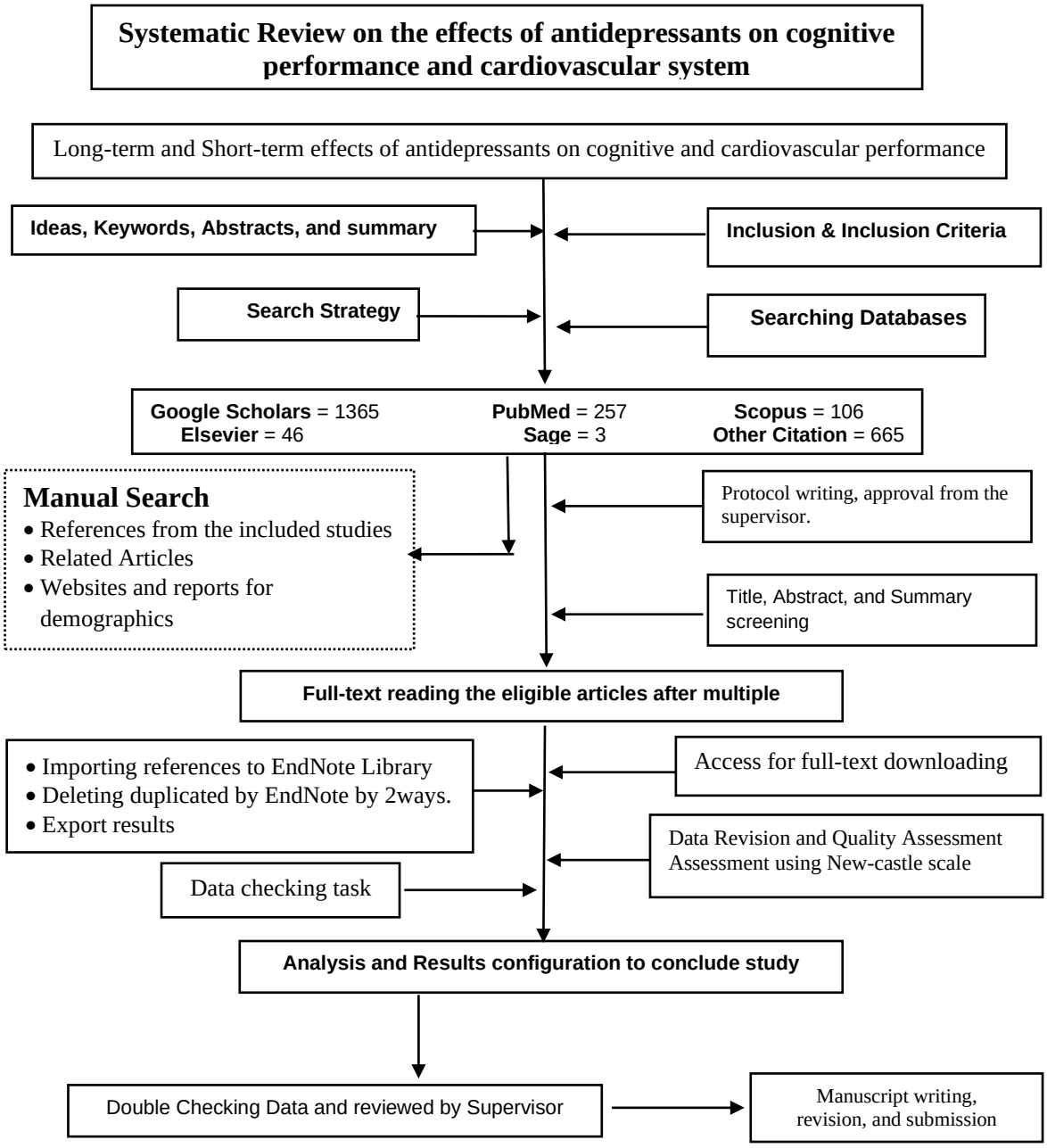

Fig: 5. Detailed Flow diagram of Systematic Review & Meta-analysis

Long-term effect of depressants on cognitive performance:

The scientific evidences found on search engines showed prevalence of the disturbed and disoriented cognitive performance effected by the continuous use of antidepressants. 12 out of selected studies showed the effect of antidepressants on cognitive performance. (n = 4) studies [43-46] proved dementia as a long-term residual effect of antidepressants. There was a link between the occurrence of dementia and any antidepressant prescription. Dementia sufferers were found to be depressed in about half of the cases. For depression-complicated dementia, doctors frequently give selective serotonin reuptake inhibitors (SSRIs). In rodents, SSRIs have impacts on brain function related to neuronal plasticity, neurogenesis, and neuronal differentiation, and they may help with cognitive performance. A history of depression was compared to be in association with increased risk of dementia, found in a longitudinal study of older men [47]. The relation between depression and incident dementia was mostly attribuTab. to cases of dementia acquired within the first 5 years of follow-up, after which the relation dissolved.

Antidepressants were associated with less psychotic symptoms, lower functional impairment, and better levels of social interaction in the antidepressant group. Depression, anxiety, bipolar disorder, and sleep difficulties were more prevalent among individuals on antidepressants than among those who were not [51]. When researchers evaluated the risk of dementia between antidepressant users and nonusers among individuals with depression, they discovered that antidepressant users had a considerably greater risk of dementia than nonusers (Risk ratio. 1.37, 95% Confidence Interval. 1.11-1.70). Whereas, Antidepressant users had a considerably greater risk of dementia than the overall population, according to research comparing dementia risk between antidepressant users and the general population (RR.$_{1\4}$ 1.31, 95% CI.$_{1\4}$ 1.15- 1.49) [45]. The choice

reaction time, crucial flicker fusion threshold, and other tests have been reported to be affected by amitriptyline, dothiepin, and trazodone [52]. Furthermore, antidepressant users tend to have remitted depression, although it is uncertain if antidepressant cognitive benefits are attribuTab. to patients' previous diagnosis of depression.

Long-term effect of depressants on cardiovascular system:

The combination of SSRI (fluoxetine, paroxetine, citalopram, escitalopram) or bupropion with metoprolol or propranolol (37.9% of cases) resulted in a significant increase in the serum concentration of the above-mentioned beta-blockers, resulting in the onset or exacerbation of such side effects associated with the use of those same medications as bradycardia, hypotension, dizziness, and in one case (combination of fluoxetine + propranolol) cardiac arrest [55]. Clopidogrel should be used with caution in individuals taking antidepressants because of the likelihood of a harmful interaction with bupropion. Three incidences of seizures were reported in the studied material after taking bupropion and clopidogrel together. The increased risk of hyponatremia is another area of interaction between antidepressants and drugs used to treat cardiovascular disorders. It generally refers to the use of SSRI and SNRI together. The serotonin transporter protein may be inhibited by SSRIs, causing serotonin absorption into platelets to be decreased; consequently, this mechanism appears to be linked to adverse effects like longer edema periods or hemorrhagic stroke [56].

Discussion

The main objective to conduct this systematic review was to understand the long-term effect of multiple antidepressants on individual's cognitive performance and cardiovascular system. Depression is linked to an

increased risk of cognitive impairment and cardiovascular disease in general. Antidepressant therapy hasn't been found to lessen the danger.

Despite the research authors' adjustments to the risk variables, it's still impossible to say if depression and/or antidepressants enhanced the risk of cognitive dissonance as claimed. Previous research, on the other hand, revealed that antidepressants might help people with depression improve their cognitive performance. In comparison to the general population, patients with depression, whether or not using antidepressants, had a greater risk of dementia. Antidepressants, particularly SSRIs, were found to cause higher cognitive deterioration and an increased risk of MCI or dementia in people who used them, regardless of their depressive symptoms.

Strong anticholinergic medications have been linked to an increased risk of cognitive deterioration [58]. TCAs were shown to have considerable anticholinergic effects when used as antidepressants. Recent case-control research found that antidepressants with significant anticholinergic qualities, such as amitriptyline and Dosulepin, along with SSRIs without any documented adverse side effects, have both been linked to a higher risk of dementia [46].

Rise in norepinephrine and serotonin levels, perhaps leading to an increase in cardiac sympathetic activity and a modestly increased heart rate with pulmonary circulation stress. Individuals may develop hypertensive, hypoglycemic episodes, and palpitations; however, the risk of ventricular arrhythmias is modest. Patients on SNRIs should have their blood pressure monitored. QRS prolongation, atrial fibrillation, atrioventricular block, ventricular tachycardia, and sudden myocardial infarction are all reported as strong anticholinergic and cardiovascular adverse effects. When compared to SSRIs, TCA usage is linked to a considerably higher risk of

stroke. Platelet activation and aggregation are inhibited by SSRIs, which can lead to a loss of homeostasis, irregular bleeding, and a higher likelihood of intracerebral hemorrhages.

There are various limitations to our research. The absence of data on the beginning and recurrence of depressive symptoms, as well as the use of antidepressants throughout follow-up, was the most evident disadvantage of our study design. Another problem to consider is confounding by indication, since antidepressants may have been administered preferentially to more severe instances of depression. The sample size was one of the study's shortcomings. Regardless matter how many study population studies are conducted; the data is insufficient to calculate for adequate population. Due to language hurdles and unrestricted access to all audiences, the studies gathered and assessed in this systematic review were solely in English. The study may be evaluated in the future using a broad set of data, and in-depth quantitative or mixed method analysis on several obesity characteristics in many populations from various socioeconomic backgrounds can be performed. There's a strong chance that data buried in other languages has additional creative information for this review research.

Conclusion

In conclusion, our review indicated that the use of antidepressants like SSRIs, TCA, SNRI, and other anticholinergic drugs have an adverse and long-term effect on cognitive performance including dementia and other psychogenic dissonance. Similarly, the prolonged use of these antidepressants showed side effects on the cardiovascular system including stroke, Hypertension and in some cases myocardial infraction. Side effects, particularly impairments of essential bodily organs, must be addressed by healthcare specialists. Regardless of that, for those who don't have

knowledge of the dosage, the physicians should educate the proper use and harmfulness of those suffering from depressive disorders. To improve the validity of results, future research should incorporate self-reported measures with data from health databases.

Appendix 1
Search strategy used in mapping against SPIDER tool

Keywords	
Sample	depress* OR Adults* OR Human*
Phenomenon of Interest	(Antidepressants OR Effects OR short-term OR Long-term OR Learning-disability OR cognitive-performance OR Dementia OR PTSD OR Cardiac OR Cardiovascular OR Myocardial-infraction OR stroke OR hypertensive [Title/Abstract] OR blood-pressure OR heart-disease OR pulmonary OR ADHD OR memory-loss OR psychological OR physiological
Evaluation	(Cognitive-performance OR Cardiovascular-system OR Myocardial Infraction OR Stroke OR Dementia
Research Type	(cohort OR prospective stud OR longitudinal stud OR follow-up Reviews OR Systematic-Reviews OR Meta-analysis*

Appendix 2
Search strategy used in Search engines like PubMed & Google Scholars

Keywords		
Sample	(depress*[Title/Abstract] OR Adults*[Title/Abstract]	AND
Variables	(Antidepressants [Title/Abstract] OR Effects [Title/Abstract] OR short-term [Title/Abstract] OR Long-term [Title/ Abstract] OR Learning-disability [Title/Abstract] OR cognitive performance [Title/Abstract] OR Dementia [Title/Abstract] OR PTSD [Title/ Abstract] OR Cardiac [Title/Abstract] OR Cardiovascular [Title/Abstract] OR Myocardial- infraction [Title/Abstract] OR stroke [Title/Abstract] OR hypertensive[Title/Abstract] OR blood pressure [Title/Abstract] OR heart-disease[Title/ Abstract] OR pulmonary[Title/Abstract] OR ADHD [Title/ Abstract] OR memory-loss [Title /Abstract] OR psychological [Title/ Abstract] OR physiological[Title/Abstract]	AND
Outcome	(Cognitive-performance [Title/Abstract] OR Cardiovascular-system [Title/Abstract]	AND
Type of study	(Cohort [Title/Abstract] OR prospective stud*[Title/Abstract] OR longitudinal stud*[Title/Abstract] OR follow-up [Title/Abstract] Reviews* [Title/Abstract] OR Systematic Reviews* [Title/Abstract] OR Meta- analysis*[Title/Abstract]	AND
Filters	(Journal Article[ptyp] AND („2016/01/01"[PDat]: „2022/01/01" [PDat]) AND English[lang])	AND

Appendix 3

The studies included in this systematic review were evaluated for quality.

First author, year	Representa-tiveness of the exposed Variable	Selection of the unexposed Variable	Ascertain-ment of exposure	Outcome of interest not present at start of study	Control for important factors or additional factors	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of Variables	Total score
46	*	*	*	*	**	*	*	*	9
48	*	*	*	*	**	*	---	---	7
49	*	*	*	*	**	*	*	*	9
47	*	*	*	---	**	*	*	*	8
50	*	*	*	*	**	*	*	*	8
51	*	*	*	---	**	*	*	*	8
45	*	*	*	*	**	*	---	---	7
44	*	*	---	*	**	*	*	*	9
43	*	*	*	*	**	*	*	*	9
52	*	*	*	*	**	*	---	---	7
53	*	*	*	---	**	*	*	*	8
54	*	*	*	*	**	*	---	*	8
55	*	*	*	*	**	*	*	*	9
56	*	*	*	*	**	*	*	*	9
57	*	*	*	---	**	*	*	*	8

Appendix 3
PRISMA Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7-8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured Tab's or plots.	8

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Appendix 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Appendix 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Appendix 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-12
	23b	Discuss any limitations of the evidence included in the review	11
	23c	Discuss any limitations of the evidence included in the review	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
Registration and protocol			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	--
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	--
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	--
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	--
Competing interests	26	Declare any competing interests of review authors.	--
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	--

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