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Atypical depression is associated with metabolic syndrome: a systematic review

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ABSTRACT

Introduction. Depression and metabolic syndrome (MetS) are important public health problems. This systematic review evaluated whether the atypical subtype of depression is associated with MetS, when compared to other depressive subtypes.

Methods. Two independent reviewers searched in Medline, Lilacs, PsycInfo, Scopus and Web of Science databases, up to May 2021, without language restriction, including cross-sectional, case-control, and cohort studies, assessing adults. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale. The PRISMA guidelines were adopted and this review was registered in PROSPERO (CRD42018109762).

Results. The databases search identified 96 articles and 6 was included in this review. The methodological quality scores ranged from 7 to 10 points. The association between atypical depression and MetS was demonstrated in all publications, as well as the lack of association with melancholic and other subtypes. The prevalence of MetS was significantly higher among individuals with atypical depression. It is worth noting that only few studies assessing this comorbidity were conducted so far.

Conclusions. MetS is associated with atypical depression, but not with melancholic or other subtypes. The identification of distinct depressive clinical features seems crucial to better understand its comorbidity with MetS and elucidate its pathophysiological pathways, both necessary to better guide prevention and treatment strategies.

Key words. Metabolic syndrome; atypical depression; depressive subtypes; systematic review; mental disorders.

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LA DEPRESIÓN ATÍPICA SE ASOCIA CON EL SÍNDROME METABÓLICO: UNA REVISIÓN SISTEMÁTICA

RESUMEN

Introducción. La depresión y el síndrome metabólico (SM) son problemas importantes de salud pública, esta revisión sistemática evaluó si el subtipo atípico de depresión está asociado con el SM, en comparación con otros subtipos depresivos.

Metodología. Dos revisores independientes realizaron búsquedas en las bases de datos de Medline, Lilacs, PsycInfo, Scopus y Web of Science, hasta mayo de 2021, sin restricción de idioma, incluidos estudios transversales, de casos y controles y de cohortes, que evaluaban a adultos. La calidad metodológica de los estudios se evaluó mediante la escala de Newcastle-Ottawa. Se adoptaron las directrices PRISMA y esta revisión tiene registró en PROSPERO (CRD42018109762).

Resultados. La búsqueda en las bases de datos identificó 96 artículos y 6 se incluyeron en esta revisión. Los puntajes de calidad metodológica variaron de 7 a 10 puntos. La asociación entre depresión atípica y SM se demostró en todas las publicaciones, así como la falta de asociación con melancólico y otros subtipos. La prevalencia de SM fue significativamente mayor entre las personas con depresión atípica. Vale la pena señalar que hasta el momento solo se han realizado pocos estudios que evalúen esta comorbilidad.

Conclusiones. SM se asocia con depresión atípica, pero no con melancólico u otros subtipos. La identificación de características clínicas depresivas distintas parece crucial para comprender mejor su comorbilidad con SM y dilucidar sus vías fisiopatológicas, ambas necesarias para orientar mejor las estrategias de prevención y tratamiento.

Palabras clave. Síndrome metabólico; depresión atípica; subtipos depresivos; revisión sistemática; desórdenes mentales.

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INTRODUCTION

Depression and metabolic syndrome (MetS) are important public health problems. Depression affects over 300 million people worldwide[1] and the prevalence of MetS is about 20 to 25% among adults[2]. However, the association between these morbidities is still poorly understood, with a bidirectional[3,4] and yet controversial association, as there were studies that showed no relationship between depression and MetS[5] or a relationship only between certain components of MetS[6].

The relationship between depression and MetS may be due to the unhealthy lifestyle adopted by depressive individuals[7] and by the deregulation of the adrenocortical and autonomic nervous systems common in both diseases[8], sharing pathophysiological mechanisms, including high levels of proinflammatory oxytocin and glucocorticoids[9].

It is known that depression may present with distinct clinical manifestations[10]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11], a depressive episode may be clinically classified as with several subtypes, including depression with melancholic, with atypical features, and others. Apart from depressive core symptoms, melancholic depression is characterized by weight loss, loss of appetite, insomnia, and feelings of excessive and inappropriate guilt, while atypical depression presents with hypersomnia, increased appetite and weight gain, and reactivity of mood[11,12].

The relationship between MetS and depression could be better understood based on this differentiated into subtypes. The aim of this study is to assess whether atypical subtype of depression is associated with MetS, compared to those with other subtypes and without depression, by a systematic review of the scientific literature.

METHODS

A systematic review was performed and the protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews), under number CRD42018109762. The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines[13] were adopted for reporting results.

Two independent reviewers (LOF and DAS) performed the search and evaluation of all articles and in case of inconsistencies, a consensus was established between them and/or with the opinion of a third reviewer (MCV). It was searched reports indexed in the MEDLINE (Pubmed), LILACS, PsycINFO, Scopus and Web of Science (ISI) databases published up to May 2021, without language or publication date restrictions. The Microsoft Excel was used to manage the references. It was used the Boolean operators to combine the keywords: *metabolic syndrome, X syndrome, depress* subtype, subtypes of depress*, types of depressive disorder, atypical features, atypical depression* e *adults*.

Studies were eligible if they were conducted among adult (18-66 years), examined atypical subtype compared to other subtypes of depression, presented original data, and had a cross-sectional, case-control, or cohort design. It was excluded studies with specific groups, such as individuals with medical/clinical conditions, pregnant or post-partum women or inpatients. Case reports, editorial articles, comments, letters, clinical trials, animal studies and reviews were also excluded.

After removing all duplicates, the selection process included the evaluation of titles and abstracts, and reading all remaining articles in full. It was extracted the information about the authors and publication date, place of study, population studied, objectives, how the presence of MetS and depression were assessed, reported measures of association and main results.

The methodological quality of studies was evaluated using the Newcastle-Ottawa Scale (NOS), which includes blocks of selection, comparability and outcomes. The total score to each study corresponds to the number of positive items, with a total of 10 points for cross-sectional studies and 9 points for those with a cohort and case-control design[14,15].

RESULTS

The database searches resulted in 96 articles, of which 25 came from Medline, 17 from PsycInfo, 27 from Lilacs, 7 from Web of Science and 20 from Scopus. Nineteen duplicated reports were removed. After evaluation by titles and abstracts, 8 papers were eligible for full reading and 6 were included in the systematic review[16-21]. The selection process of the articles is detailed in Figure 1.

All 6 publications included in this review are related to studies conducted after 2010. All studies had large sample sizes, with over 700 participants, most of the studies included male and female individuals (5/6), and regarding study design, half of them were cross-sectional, 2 were case-control and 1 had a cohort design. These publications are the result of just three different studies carried out in different countries: the NESDA study (Netherlands Study of Depression and Anxiety) from Netherlands (3/6), the CoLaus study (Cohort study of Lausanne) from Switzerland (2/6) and another from Japan (1/6). The main methodological aspects

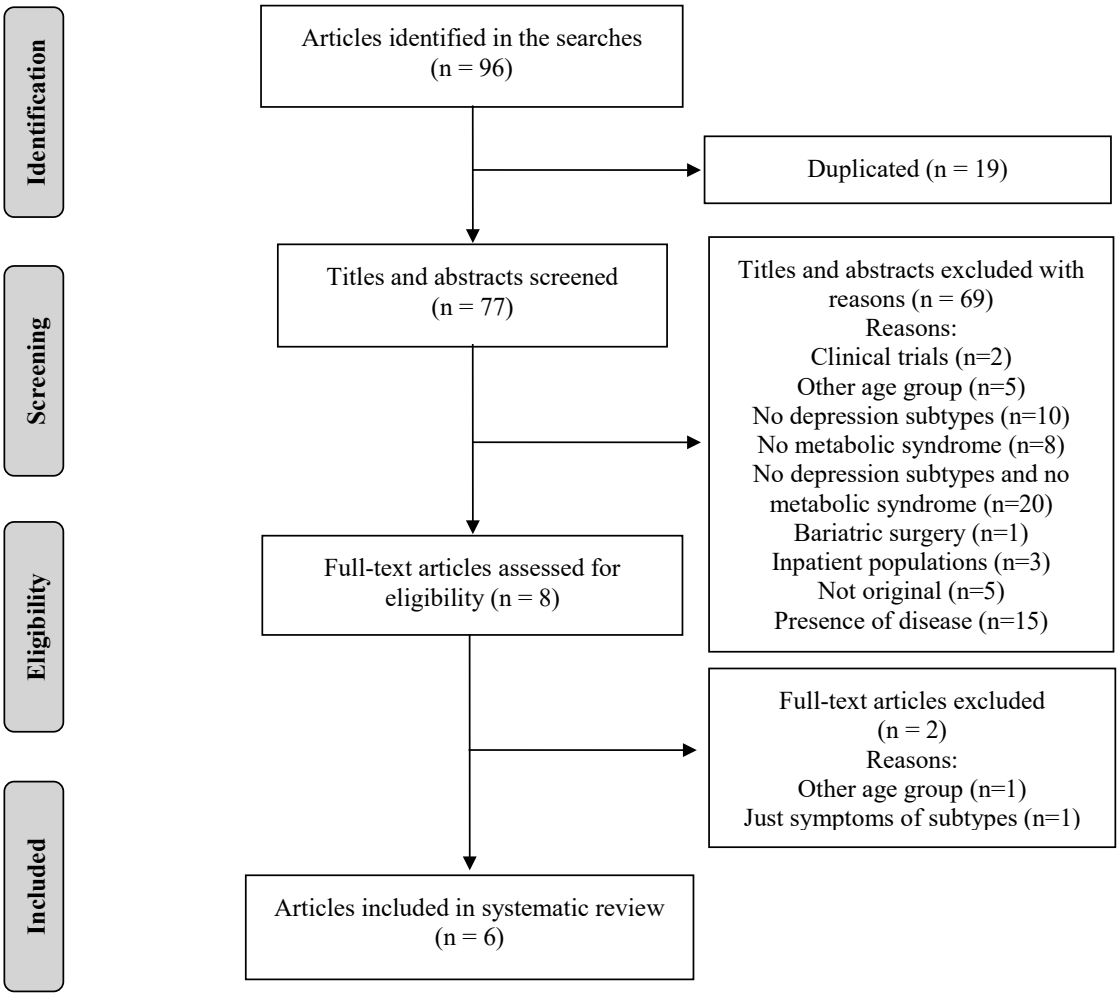

Figure 1 Flow diagram for the search results

of the publications are presented in Table 1.

In most studies (5/6), the diagnosis of MetS was based on the Adult Treatment Panel III. Depression subtypes classification was performed using two methods, either through latent class analysis (3/6) or symptoms assessment based on the DSM-IV[22] diagnostic criteria (3/6) (Table 1). All studies evaluated depression through validated diagnostic instruments, using the Composite International Diagnostic Interview (CIDI) (3/6), the Diagnostic Interview for Genetic Studies (DIGS) (2/6) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (1/6).

The objectives of the articles, measures of associations and results of interest are presented in Table 2. Each report had different aims, it is noteworthy mention that the association between depression subtypes and MetS was the main objective of only one of them. Odds Ratios were the most common measure of associations (4/6).

Adjustment variables, statistical methods and ways of comparing depressive subtypes also varied among the studies. The association between atypical depression and MetS was demonstrated in all publications, as well as the lack of association with melancholic depression. In most studies, the prevalence of MetS was significantly higher among subjects with atypical depression compared to those with melancholic depression or other subtype (Table 2).

In the CoLaus study, Glaus et al[16] evaluated this association by three different models, progressively adjusting for an increasing number of variables. In models 1 and 2 the

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Table 1 Details of the selected studies included in the systematic review

Study	Country	Author/Year	Design	Sample	Metabolic Syndrome Criteria	Specifiers Depression Subtypes
CoLaus	Switzerland	Glaus et al. (2013)	Cross-sectional	3,716 subjects, aged 35-66 years	Adult Treatment Panel III	DSM-IV
		Lasserre et al. (2016)	Cohort	2,813 subjects, aged 35-66 years	Adult Treatment Panel III	DSM-IV
NESDA	Netherlands	Lamers et al. (2010)	Cross-sectional	818 subjects, aged 18-65 years	Adult Treatment Panel III	Latent Class Analyses
		Lamers et al. (2013)	Case-control	776 subjects (233 cases – 111 melancholic depression and 122 atypical / 543 controls), aged 18-65 years	Adult Treatment Panel III	Latent Class Analyses
		Lamers et al. (2016)	Nested case-control within a 6-year cohort study	1,248 subjects (648 cases – 308 melancholic depression and 167 atypical / 600 controls), aged 18-65 years	Adult Treatment Panel III	Latent Class Analyses
-	Japan	Takeuchi et al (2013)	Cross-sectional	1,011 male office workers, aged 20-59 years	International Diabetes Federation	DSM-IV

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

association of atypical depression and MetS was significant (OR 1.6 and 1.8, respectively). With additional adjustment for use of psychotropic drugs and cardiovascular/behavioral risk factors (final model), the magnitude of association between atypical depression and MetS remained high, but reached the threshold of statistical significance (OR 1.6; 95% CI 1.0-2.4). Melancholic depression was not associated with MetS in all models tested.

Similar and even more robust results were reported by Lasserre et al[21], as atypical depression was significantly associated with the incidence of MetS over a 5.5-year follow-up period, even after adjusting for models 1 and 2 proposed by the authors (OR 2.4 and 2.6, respectively), and remained so (OR 2.5) when inflammatory markers and adipokine levels were added in the adjustment. Using the same analytical methods, melancholic depression was not associated with MetS (Table 2).

In the NESDA study reported by Lamers et al[17], using latent class analyses to identify depression subtypes, the prevalence of MetS was higher among individuals with atypical depression compared to melancholic depression, with over a two-fold higher chance of association with MetS in the atypical subtype (Table 2). When assessing separate components for MetS diagnostic criteria, large waist circumference (>102 cm for men and 88 cm for women) and high triglyceride levels (≥1.7 mmol/L) were more prevalent among individuals with atypical depression (OR 2.3; 95%CI 1.59-3.35 and OR 1.9; 95%CI 1.25-2.99, respectively).

In a follow-up article from the NESDA study reported by Lamers et al[18], the diagnosis of MetS was not considered in the analyzes, but, instead, the number of separate components of MetS diagnostic criteria was used. A higher number of MetS components was significantly more frequent in atypical depression compared to both the melancholic subtype and the control group (Table 2).

In a subsequent paper of the same cohort, Lamers et al[19] evaluated the incidence rates of MetS over a 6-year follow-up period. Worse outcomes over time were observed in individuals with atypical depression compared to those with all other subtypes assessed, including melancholic depression (Table 2). They had significantly higher prevalence rates of MetS and a larger number of MetS components in the baseline. From graphic information presented in the article, a trend of increasing prevalence of MetS and number of MetS components were observed over time, with higher rates in atypical depression compared to all other types, measured at baseline, 2-year and 6-year follow-up (Table 2).

In a study of Japanese male office workers, Takeuchi et al[21] compared the prevalence rates of MetS in respondents with regard to depression classified into three groups: with atypical depression, with non-atypical depression and

Table 2 Main results of the selected studies in the systematic review

Study	Author/ Year	Primary objective(s) of study	Measure(s)	Results
CoLaus	Glaus et al. (2013)	- To assess the associations between mood, anxiety and substance use disorders, including their subtypes, and the prevalence of cardiovascular risk factors	*Odds Ratio* (OR)	*- Adjusted for demographic characteristics* Atypical and MetS: OR=1.6; 95%CI 1.1-2.4 Melancholic and MetS: OR=1.2; 95%CI 0.9-1.7 Unspecified and MetS: OR=0.8; 95%CI 0.6-1.0 p<0.05 *- Adjusted for demographic characteristics and all mental disorders* Atypical and MetS: OR=1.8; 95%CI 1.2-2.6 Melancholic and MetS: OR=1.3; 95%CI 0.9-1.8 Unspecified and MetS: OR=0.9; 95%CI 0.6-1.2 p<0.01 *- Adjusted for demographic characteristics, comorbid disorders, behavioral cardiovascular risk factors and psychotropic medication* Atypical and MetS: OR=1.6; 95%CI 1.0-2.4 Melancholic and MetS: OR=1.3 95%CI 0.9-1.8 Unspecified and MetS: OR=0.8; 95%CI 0.6-1.1 p<0.05
	Lasserre et al. (2016)	- To assess the prospective associations of the atypical, melancholic and unspecified subtypes of depression with changes of fasting glucose, high-density lipoprotein-cholesterol, triglycerides, systolic blood pressure and the incidence of metabolic syndrome - To determine the potential mediating role of inflammatory marker or adipokine concentrations, eating behaviors and changes in waist circumference during follow-up	*Odds Ratio* (OR)	*- Adjusted for age and gender* Atypical and MetS: OR=2.4; 95%CI 1.5-3.6 Melancholic and MetS: OR=0.9; 95%CI 0.6-1.4 Unspecified and MetS: OR=1.0; 95%CI 0.8-1.4 p<0.001 *- Adjusted for sociodemographic characteristics, length of follow-up, behavioral factors, comorbid disorders, early trauma, depression status at baseline and follow-up, medication at baseline and cardio-metabolic risk factors at baseline (Model 1)* Atypical and MetS: OR=2.6; 95%CI 1.3-4.9 Melancholic and MetS: OR=1.5; 95%CI 0.8-2.7 Unspecified and MetS: OR=1.0; 95%CI 0.8-1.4 p<0.01 *- Model 1 additionally adjusted for inflammatory marker and adipokine concentrations at baseline (Model 2)* Atypical and MetS: OR=2.5; 95%CI 1.3-4.8 Melancholic and MetS: OR=1.5; 95%CI 0.8-2.7 Unspecified and MetS: OR=1.4; 95%CI 0.8-2.5 p<0.01
			Prevalence (%)	*- Prevalence of MetS at baseline:* Atypical: 22.4% Melancholic: 17.1% Unspecified: 15.9% No depression: 19.5% p: not significant
NESDA	Lamers et al. (2010)	- To identify empirically valid subtypes of depressive disorder on the basis of depressive symptomatology - To test whether these subtypes yield meaningful categories in terms of underlying risk factors, comorbidity patterns, and clinical characteristics	*Odds Ratio* (OR)	*- Association with MetS, adjusted for clinical psychiatric, demographic, psychosocial and physical health* Atypical *vs* Melancholic: OR=2.2; 95%CI 1.4-3.4
			Prevalence (%)	*- Prevalence of MetS:* Atypical: 25.5% Melancholic: 15.5% Atypical *vs* Melancholic: p<0.004

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	Lamers et al. (2013)	- To compare different pathophysiological indicators of hypothalamic–pituitary–adrenal axis function, the inflammatory response system and metabolic syndrome across these two subtypes of depression and healthy controls	Mean and Standard Deviation	- *No. of MetS components* - *Without adjustment* Atypical: 1.8 (1.4) Melancholic: 1.4 (1.2) Controls: 1.4 (1.3) Atypical *vs* Melancholic: p=0.01 Atypical *vs* Control: p=0.01 - *Adjusted for sex, age, educational level and smoking* Atypical: 1.8 (0.1) Melancholic: 1.3 (0.1) Controls: 1.4 (0.0) Atypical *vs* Melancholic: p<0.0001 Atypical *vs* Control: p=0.001
	Lamers et al. (2016)	- To compare the course of atypical, melancholic and moderate depressive subtypes in psychiatric course indicators such as presence of psychiatric diagnoses, suicidality and differences in BMI and metabolic syndrome during a 6-year follow-up	Prevalence (%) Mean and Standard Deviation	- Prevalence of MetS: *baseline* Atypical: 31.1% Melancholic: 20.2% Moderate: 19.3% Atypical *vs* Melancholic *vs* Moderate: p=0.01 - *No. of MetS components*: *baseline* Atypical: 2 (1-3) Melancholic: 1 (1-2) Moderate: 2 (1-2) Atypical *vs* Melancholic *vs* Moderate: p=0.02 - *Prevalence of* MetS*: follow-up* Increasing estimates over time (2-year and 6-year) Higher rates in atypical *vs* other types: p<0.05 - *Number of MetS components*: *follow-up* Increasing components over time (2-year and 6-year) Higher number in atypical *vs* other types: p<0.05
-	Takeuchi et al. (2013)	- To clarify the correlation between MetS and depression, considering atypical features of depression among male office workers	*Odds Ratio* (OR)	- *Association with Mets* - *Without adjustment* Atypical *vs* no depression: OR=2.6; 95%CI 0.8-8.3 Non-atypical *vs* no depression: OR=1.5; 95%CI 0.7-3.2 - *Adjusted for age* Atypical *vs* no depression: OR=3.1; 95%CI 0.9-10.3 Non-atypical *vs* no depression: OR=1.5; 95%CI 0.7-3.1 - *Adjusted for age, history of cardiovascular disease, type 2 diabetes, anxiety, and four lifestyle habits (smoking status, alcohol consumption, exercise, and sleeplessness* Atypical *vs* no depression: OR=3.8; 95%CI 1.1-13.2 Non-atypical *vs* no depression: OR=1.6; 95%CI 0.7-3.6

MetS: Metabolic Syndrome; OR: Odds Ratio; CI: Confidence Interval.

without depression. The prevalence of MetS was higher in those with atypical depression, compared with the non-atypical and without depression groups, but this difference was not significant (p=0.07) (graphic data in the publication, not described in Table 2). The association with MetS was significant in the atypical depression group in adjusted multiple analytical models.

Assessment of the methodological quality (NOS) and individual scores for all features assessed according to the study design are described in Table 3. None of the case-control nor the cohort studies scored in all criteria assessed, but one cross-sectional study reached the maximum score. Overall, all studies scored highly in methodological quality, and total scores ranged from 7 to 10 points. In the cross-sectional and case-control studies, the limitations observed were the lack of representativeness of samples or the cases, and the lack of information regarding non-response rates. In the cohort study, the only limitation observed was the lack of information regarding the presence of outcomes at the beginning of the study (Table 3).

DISCUSSION

This systematic review found different distribution patterns and association of MetS and depression subtypes. Atypical depression was associated with MetS in all studies and such association was not observed with the melancholic subtype.

Table 3 Assessment of methodological quality according to study design: (A) cross-sectional, (B) cohort and (C) case-control. (NOS)

Author / Year (A)	Selection				Comparability	Outcome		Total Score (Max=10)
	Representativeness of the sample (0-1)	Sample size (0-1)	Non-respondents (0-1)	Ascertainment of exposure (0-2)	Control for important factor or additional factor (0-2)	Assessment of outcome (0-2)	Statistical test (0-1)	
Glaus et al. (2013)	1	1	0	2	2	2	1	9
Lamers et al. (2010)	1	1	1	2	2	2	1	10
Takeuchi et al (2013)	0	1	1	2	2	2	1	9

Author / Year (B)	Selection				Comparability	Outcome			Total Score (Max=9)
	Representativeness of the exposed cohort (0-1)	Selection of the non-exposed cohort (0-1)	Ascertainment of exposure (0-1)	Outcome of interest was not present at start of study (0-1)	Control for important factor or additional factor (0-2)	Assessment of outcome (0-1)	Was follow-up long enough for outcomes to occur (0-1)	Adequacy of follow-up of cohorts (0-1)	
Lasserre et al. (2016)	1	1	1	0	2	1	1	1	8

Author / Year (C)	Selection				Comparability	Outcome			Total Score (Max=9)
	Adequate definition of the cases (0-1)	Representativeness of the cases (0-1)	Selection of controls (0-1)	Definition of controls (0-1)	Control for important factor or additional factor (0-2)	Ascertainment of exposure (0-1)	Same method of ascertainment for participant (0-1)	Non-response rates (0-1)	
Lamers et al. (2013)	1	0	1	1	2	1	1	1	8
Lamers et al. (2016)	1	1	1	1	1	1	1	0	7

There are several strengths in this study. It is the first systematic review that investigates the association between different subtypes of depression and MetS. Papers published in several databases were included, without any restrictions of language and publication date. Most of the studies were carried out with representative samples of the population, from different parts of the world, with good methodological quality, ensuring the reliability of results.

It was observed in the study by Glaus et al[16] that, by inserting the use of psychotropic medication as an adjustment variable, the strength of the association between atypical depression and MetS was reduced, but remained statistically significant. It is well documented that several antidepressant medications can lead to weight gain[23] and that obesity is associated with both atypical depression[24] and MetS[25].

A slight reduction in the magnitude of association between atypical depression and MetS was also reported by Lasserre et al[20] when inflammatory markers and adipokine levels were added in the models, supporting the hypothesis that depression and MetS may have common physiopathogenic mechanisms associated with inflammation. However, as evidence suggests that these associations are specific to atypical depression, Lamers et al[26] investigated if MetS and inflammatory markers were associated with individual depressive symptoms that are part of the atypical and non-atypical depressive clinical profiles, in 808 participants of the NESDA study. They found that increased appetite (atypical depression) and insomnia (non-atypical) were positively associated with number of MetS components. However, only increased appetite, within a depressive episode, was associated with metabolic and inflammatory markers, suggesting that it could be a key feature of an immuno-metabolic form of depression, as it is the most important symptom driving associations of depression with BMI, metabolic syndrome and inflammation. As depressive symptoms were not clustered into subtypes of depression, this publication was not included in this systematic review.

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Depression and MetS have been reported to be associated with cardiovascular diseases (CVD)[27,28]. Vaccarino et al[29] investigated whether MetS and its components would explain, entirely or in part, the reported association between depression and CVD among participants of the Women's Ischemia Syndrome Evaluation (WISE). They found that depression and MetS are independently associated with each other, regardless of other factors related to lifestyle and functional status. However, the MetS explained only 20% of the association between depression and incident CVD over a 5.9 year-follow-up period, suggesting that both increase the risk of CVD, mainly through independent pathways. As the sample studied included only women with suspected coronary artery disease, it is possible that the associations of depression and CVD were stronger, due to the probable oversampling of atypical depressive cases, the depression subtype most importantly associated with MetS and cardiovascular risk.

In this review, it was demonstrated that the prevalence rates of MetS were higher in participants with atypical depression, when compared with those presenting other clinical subtypes or without depression in most studies. On the other hand, Vanhala et al[30] evaluated the risk of developing MetS in the presence of depressive symptoms, comparing melancholic with other depressive features. The risk was higher among women with more frequent melancholic symptoms at the study baseline compared with women with non-melancholic depression. However, "changes in sleeping and appetite" were considered when creating the group of melancholic symptoms, and it is not clear whether any changes were included or only decreased appetite and sleeping, which are part of the melancholic depression. Therefore, misclassification cannot be ruled out and this melancholic subgroup may have erroneously included cases of atypical depression. This study was not included in the present systematic review since the diagnosis of the atypical depression subtype was not evaluated.

A few limitations of this systematic review have to be considered. The only cohort study included has not allowed to infer causality between the variables of interest (although assessed and made available) as this was not the main aim of the study. This highlights the need of more longitudinal investigations to understand and disentangle the associations found. Only few studies could be included in this systematic review, as most reports available used different forms of classifying depressive profiles or had no ascertainment of the atypical subtype, which may impair the diagnostic equivalence of clustered subtypes. This could also have prevented the detection of associations between MetS and other subtypes of depression.

An additional point to be raised is although this review includes six publications, these are the result of only three different studies, restricting the variety of the populations analyzed. However, different methods of analysis and comparisons were used in the same populations and yet the association with MetS was only observed in atypical depression when compared with melancholic or other subtypes. Finally, due to few publications were found in the searches and included in this review, it was not possible to carry out a meta-analysis of the available data.

The lack of diagnostic tools to identify and differentiate depression subtypes was also evidenced. The methods used were designed to the identification of depressive symptoms or the diagnosis of a depressive episode. Screening scales and structured diagnostic instruments were used, with a subsequent classification into subtypes based upon grouping of characteristic symptoms or identifying profiles through statistical cluster analyzes. The subtypes according to specific clinical profiles, such as melancholic, were incorporated in the third edition of the DSM (DSM□III)[31] as specifiers of major depressive disorder. Atypical depression was included in the DSM□IV[22], but both specifiers remained in the DSM□5[11]. Some studies included in this review used DSM-IV in the classification of subtypes, but there would be no impact on the classification of subtypes when considering DSM-5, because the DSM-5 does not introduce changes in the diagnostic criteria for major depression and its subtypes, with only the addition of specifiers "mixed" and "anxious"[11]. It is important to emphasize that the diagnosis of depression subtypes according the presence of different symptom profiles included in the DSM as specifiers has not been incorporated by the World Health Organization International Classification of Diseases criteria. Indeed, there is not yet a global consensus on differentiating depression into discriminant subtypes[32].

All articles included in this review were published within the last decade, indicating a rather recent interest in the subject, and unveiling the scarcity of data available and the need to disentangle the nature of the association between MetS and depression, as it is still unclear and controversial[33,34]. The results presented herein demonstrate the relevance of identifying distinct subtypes of depression, according to specific symptom profiles. Atypical depression was significantly associated with MetS and some MetS components, deserving attention due to its clinical importance. The identification of depressive subtypes could support differential preventive and treatment strategies in the presence of increased risk for CVD or inflammation-related comorbidities as MetS.

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DECLARATION OF INTEREST STATEMENT

The authors declare no conflict of interest.

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