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Association of major depressive disorder with chronic diseases and multimorbidity in Brazilian adults, stratified by gender: 2019 National Health Survey

Associação do transtorno depressivo maior com doenças crônicas e multimorbidade em adultos brasileiros, estratificada por sexo: Pesquisa Nacional de Saúde 2019

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ABSTRACT: ***Objective:*** To analyze the association of major depressive disorder with chronic non-communicable diseases and multimorbidity in Brazilian adults, stratified by gender, as well as examine the interaction between gender and chronic non-communicable diseases in association with major depressive disorder. ***Methods:*** Based on a sample of 65,803 adults from the 2019 National Health Survey, we estimated the prevalence of major depressive disorder (≥10 points in the Patient Health Questionnaire) according to the presence of chronic non-communicable diseases and multimorbidity (≥2 chronic diseases). Prevalence ratios and their respective confidence intervals were calculated by Poisson regression, and multiplicative interaction terms were used to assess the role of gender in the associations. ***Results:*** The prevalence of major depressive disorder among Brazilian adults (18–59 years) was 10.9%, with a statistically significant difference between men (6.0%) and women (15.4%) (p<0.001). Individuals with any chronic non-communicable disease and multimorbidity showed a higher prevalence of major depressive disorder, both in the general population and in each gender. However, the association of major depressive disorder with chronic non-communicable diseases tended to be stronger among men. Data also showed an interaction between the male gender and multimorbidity or specific diseases, such as arthritis or rheumatism, heart disease, and chronic kidney disease, in association with major depressive disorder. ***Conclusion:*** The results reveal a significant association between major depressive disorder and chronic non-communicable diseases in both genders and raise the hypothesis that the effects of multimorbidity and certain diseases may be greater on the mental health of men.

Keywords: Depressive disorder. Chronic disease. Multimorbidity. Health surveys.

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RESUMO: ***Objetivo:*** Analisar a associação do transtorno depressivo maior com a presença de doenças crônicas não transmissíveis e multimorbidade em adultos brasileiros, estratificada por sexo, e examinar a interação entre sexo e doenças crônicas não transmissíveis na associação com o transtorno depressivo maior. ***Métodos:*** Com base em amostra de 65.803 adultos da Pesquisa Nacional de Saúde de 2019 foram estimadas as prevalências de transtorno depressivo maior (≥10 pontos do instrumento *Patient Health Questionnaire*) segundo a presença de doenças crônicas não transmissíveis e multimorbidade (≥2 doenças crônicas). As razões de prevalência e os respectivos intervalos de confiança foram estimados por meio da regressão de Poisson, e os termos de interação multiplicativa foram utilizados para avaliar o papel do sexo nas associações. ***Resultados:*** A prevalência de transtorno depressivo maior entre adultos brasileiros (18–59 anos) foi estimada em 10,9%, com diferença estatisticamente significante entre homens (6,0%) e mulheres (15,4%) (p<0,001). Entre os indivíduos com quaisquer doenças crônicas não transmissíveis e multimorbidade foram observadas prevalências mais elevadas de transtorno depressivo maior, tanto na população geral como em cada sexo. Entretanto, a associação do transtorno depressivo maior com as doenças crônicas não transmissíveis tendeu a ser mais forte entre os homens. Os dados também mostraram interação entre sexo masculino e multimorbidade ou doenças específicas como artrite ou reumatismo, doença cardíaca e insuficiência renal crônica na associação com o transtorno depressivo maior. ***Conclusão:*** Os resultados revelam expressiva associação entre transtorno depressivo maior e doenças crônicas não transmissíveis, em ambos os sexos, e levantam a hipótese de que o efeito da multimorbidade e de certas doenças pode ser maior na saúde mental dos homens.

Palavras-chave: Transtorno depressivo. Doença crônica. Multimorbidade. Inquéritos epidemiológicos.

INTRODUCTION

In the world population, the proportion of individuals with depression was estimated at 4.4%, representing an increase of 18.4% between 2005 and 2015. This percentage corresponds to more than 300 million individuals[1]. The risk of depression increases with factors such as poverty, unemployment, stressful events, physical illness, and unhealthy behaviors. For almost three decades (1990–2017), depressive disorders remained among the three main causes of non-fatal health loss, measured through years lived with disability (YLD)[2].

Major depressive disorder (MDD) is characterized by broad symptomatology, including depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt, impotence, low self-esteem, sleep or appetite changes, and difficulty concentrating. These symptoms can become chronic or recurrent, interfering with the capacity for self-care and the maintenance of social, work, or domestic activities[3]. According to some studies, symptoms may vary between genders. Women with depression usually report depressed mood, anxiety disorder, and appetite, weight, and sleep disorders, while alcohol and drug abuse is more common among depressed men[4-7].

Additionally, women tend to mention more depressive symptoms and with higher frequency than men in different populations[8]. The estimate of MDD in women is generally twice that observed among men, and these differences remain throughout life, despite the variation in magnitude, reaching their peak in adolescence and stability in adulthood. Nonetheless, this does not mean that depression in men should be considered less important. A possible negative consequence of emphasizing the prevalence of women with depression is stereotyping the disease, leading to overdiagnosis of women and underdiagnosis of men[9].

Several factors may explain sex or gender disparities in the incidence and prevalence of MDD. Aspects such as social role overload, greater exposure to stressful life events, financial difficulties, in addition to genetic and biological differences, make women more vulnerable to depression[10-12], while factors such as informal work and living alone can increase the risk of depression in men[12]. Social support, in turn, can be considered a protective factor against depression for both genders[13].

Another important risk factor for depression is the presence of chronic non-communicable diseases (NCDs), but, despite the evidence of this association in the general population[14-16], the effect of gender on this relationship remains unclear. The literature review identified two studies that analyzed the interaction between gender and psychological factors in the development of heart diseases[17,18]. However, no work was found in the opposite direction, with analyses of possible differential effects of the interaction between gender and NCDs on the incidence or prevalence of depression.

Considering this gap in the literature, the present study aimed to investigate the association of MDD with NCDs and multimorbidity in Brazilian adults, stratified by gender. Specifically, we examined the interaction between gender and determined NCDs or multimorbidity in association with MDD.

METHOD

This population-based cross-sectional study used the database from the Brazilian National Health Survey (*Pesquisa Nacional de Saúde* — PNS), conducted by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* — IBGE) together with the Ministry of Health. PNS data were collected in 2019, in a probabilistic sample of the Brazilian population, selected through a three-stage cluster sampling process, with stratification of primary sampling units (PSU). The first stage selected census tracts or sets of tracts that constituted the PSU; the second consisted of choosing the households; the third selected a resident aged 15 years or older to answer the specific questionnaire. In each stage, the draw was made by simple random sampling. As part of IBGE's Integrated Household Research System (*Sistema Integrado de Pesquisas Domiciliares* — SIPD), PNS used the master sample to select primary units. PNS administered three questionnaires: one concerning household characteristics, another related to the household residents, and the third with information about the selected resident[19].

The households visited amounted to 94,114. A total of 90,846 selected residents were interviewed on their health status, lifestyle, and chronic diseases. This study only analyzed data from selected residents aged 18 to 59 years, comprising a sample of 65,803 individuals. Another publication[19] provides further details on the sampling process, the weighting, and other methodological aspects.

MDD was identified through the Patient Health Questionnaire-9 (PHQ-9), an instrument validated in Brazil[20], composed of nine questions that assess the frequency of depressive symptoms in the previous two weeks. Symptoms consist of sleep problems, fatigue or lack of energy, loss of interest or pleasure in doing things, concentration problems, food issues (poor appetite or overeating), slowness or restlessness to move or speak, depressive mood (feeling down or hopeless), feelings of failure or of having disappointed the family, and suicidal thoughts. The frequency of symptoms in the reference period was evaluated for each question, ranging from zero (not at all) to three (nearly every day) points. The maximum score is 27 points, and individuals with ten points or more were considered the most likely to have MDD. This is the score that maximizes the sensitivity and specificity of the test[21].

The main independent variable of interest was the presence of NCDs. Adults were asked whether a doctor had ever diagnosed them with the following diseases: hypertension, diabetes, heart disease, cerebrovascular accident (CVA), asthma or asthmatic bronchitis, arthritis or rheumatism, chronic back pain, work-related musculoskeletal disorder (WMSD), chronic lung disease, cancer, or chronic kidney disease. Each question had two possible answers (yes or no). The interviewees were also asked to what extent these diseases or their complications limited their routine activities (such as working, doing household chores, etc.), with the following response options: no limitation, slightly, moderately, severely, and very severely. Additionally, the number of chronic diseases reported by the interviewees was calculated and categorized as: zero, one, two, three, and four or more. Multimorbidity was defined as the presence of two or more NCDs[22]. Gender and age were used as control variables. Also, in order to evaluate the interactions, variables were built by the multiplication of each chronic disease (reference category: without NCDs) or multimorbidity and gender (reference categories: without multimorbidity and female gender, respectively).

Prevalence, prevalence ratios (PR), and 95% confidence intervals (95%CI) of MDD were estimated according to the presence or absence of each NCD and to the number of diseases and multimorbidity for the total population and by gender. The association between MDD and chronic diseases was also calculated based on the degree of limitation of NCDs. PR was obtained through multiple Poisson regression with adjustments for gender and age. Multiplicative interaction terms were used to evaluate the role of gender in the association between MDD and specific chronic diseases, as well as concerning the number of NCDs and multimorbidity. The analyses were adjusted for age, and the results were considered statistically significant when their p-values were less than 0.05. We conducted the analyses in the Stata 14.0 statistical software, taking into account the effect of the sampling plan, non-response rates, and post-stratification weights.

The National Research Ethics Committee (*Comissão Nacional de Ética em Pesquisa* — CONEP)/National Health Council (*Conselho Nacional de Saúde* — CNS) approved PNS, under the opinion no. 3,529,376, issued on August 23, 2019.

RESULTS

Data from 65,803 individuals were analyzed; their mean age was 38.1 years (95%CI 37.9–38.2), with a predominance of females (52.2%). Approximately 40% (95%CI 39.5–41.0) of adults (18–59 years) reported at least one NCD, and 14.1% (95%CI 13.6–14.6) had multimorbidity. The most prevalent diseases were chronic back pain (19%; 95%CI 18.4–19.6), hypertension (17%; 95%CI 16.4–17.5), and asthma or asthmatic bronchitis (5.5%; 95%CI 5.1–5.8). The remaining diseases were reported by less than 5% of the adult population.

Based on the PHQ-9 instrument, the prevalence of MDD among Brazilian adults was 10.9% (95%CI 10.4–11.3), with a statistically significant difference between genders: 15.4% (95%CI 14.6–16.1) in women and 6.0% (95%CI 5.5–6.5) in men. Among the adults identified with MDD by the PHQ-9, 37.0% (95%CI 34.9–39.1) reported having received a clinical diagnosis of this disease at some point in their lives.

The prevalence of MDD was higher among individuals who reported any studied NCD compared to those who had no such diseases. The most significant differences in the prevalence of MDD were detected among adults who declared being diagnosed with chronic lung disease (PR=2.82; 95%CI 2.30–3.47), CVA (PR=2.78; 95%CI 2.25–3.44), chronic back pain (PR=2.40; 95%CI 2.22–2.59), and heart disease (PR=2.33; 95%CI 2.03–2.66) in relation to those who did not present these morbidities. In addition, we identified that the prevalence of MDD increased with the number of chronic diseases, resulting in a PR=6.84 (95%CI 5.92–7.91) among interviewees with four or more chronic diseases compared to those without morbidities. The findings of this study also revealed a strong association between multimorbidity and MDD (Table 1).

Table 2 shows the prevalence ratios of MDD according to the degree of limitation of the diseases. The data demonstrated that groups reporting a greater degree of limitation in the performance of the routine activities due to chronic diseases also presented higher prevalence rates of MDD compared to those without disease.

Tables 3 and 4 describe the data stratified by prevalent gender and PR of MDD according to the presence and number of chronic diseases. We found that the prevalence of MDD was higher among women who reported chronic diseases than among men in the same condition (compared to their respective groups without the disease). However, for almost all diseases, age-adjusted PR values were higher among men, except for chronic lung disease. A statistically significant interaction was identified between males and the following chronic diseases: heart disease (PR=1.53; 95%CI 1.08–2.15); arthritis or rheumatism (PR=1.69; 95%CI 1.23–2.33), and chronic kidney disease (PR=1.79; 1.10–2.89). Both genders showed a positive gradient between the prevalence of MDD and the number

Table 1. Prevalence and prevalence ratio of major depressive disorder according to the presence of chronic diseases in Brazilian adults (18–59 years). National Health Survey, 2019 (n=65,803).

Chronic diseases	n*	Prevalence of MDD (95%CI)**	PR[a] of MDD (95%CI)**
Hypertension	11,391	17.1 (15.9–18.3)	1.65 (1.51–1.80)
Diabetes	3,053	22.0 (19.3–24.9)	1.95 (1.71–2.23)
Heart disease	1,987	25.5 (22.5–28.8)	2.33 (2.03–2.66)
Cerebrovascular accident	703	32.3 (25.8–39.6)	2.78 (2.25–3.44)
Asthma or asthmatic bronchitis	3,311	20.8 (18.3–23.5)	1.90 (1.67–2.15)
Arthritis or rheumatism	3,174	27.3 (24.4–30.3)	2.27 (2.01–2.56)
Chronic back pain	12,412	21.3 (20.1–22.6)	2.40 (2.22–2.59)
Work-related musculoskeletal disorder	1,350	20.8 (17.7–24.4)	1.70 (1.45–2.00)
Chronic lung disease	671	31.3 (24.6–38.8)	2.82 (2.30–3.47)
Cancer	894	24.3 (20.0–29.2)	1.87 (1.54–2.26)
Chronic kidney disease	751	26.0 (21.2–31.6)	2.27 (1.84–2.81)
Number of chronic diseases			
0	39,364	6.8 (6.3–7.3)	1
1	17,423	12.7 (11.8–13.7)	1.94 (1.75–2.15)
2	6,075	19.7 (18.0–21.5)	3.00 (2.67–3.37)
3	2,019	29.3 (25.8–33.1)	4.38 (3.76–5.09)
4 or +	922	46.6 (40.6–52.6)	6.84 (5.92–7.91)
Multimorbidity[b]	9,016	24.7 (23.2–26.3)	3.67 (3.32–4.05)

MDD: major depressive disorder; PR: prevalence ratio. Bold values are statistically significant. *Number of individuals in the non-weighted sample; **95%CI: 95% confidence interval; [a]prevalence ratio adjusted for gender and age (reference category: does not have the disease); [b]≥2 chronic diseases.

Table 2. Prevalence ratio of major depressive disorder according to the degree of limitation of chronic diseases in Brazilian adults (18–59 years). National Health Survey, 2019 (n=65,803).

Chronic diseases	Degree of limitation		
	None	Low/moderate	Severe/very severe
	PR[a] of MDD (95%CI)*		
Hypertension	1.17 (1.03–1.33)	2.68 (2.39–3.02)	5.58 (4.78–6.53)
Diabetes	1.44 (1.19–1.74)	2.77 (2.30–3.33)	4.66 (3.49–6.21)
Heart disease	1.54 (1.24–1.91)	2.80 (2.27–3.46)	5.11 (4.06–6.43)
Cerebrovascular accident	1.75 (1.33–2.30)	3.81 (2.72–5.35)	4.59 (3.33–6.34)
Asthma or asthmatic bronchitis	1.56 (1.31–1.85)	2.24 (1.81–2.79)	3.36 (2.65–4.27)
Arthritis or rheumatism	1.34 (1.00–1.79)	2.17 (1.83–2.57)	4.21 (3.65–4.86)
Chronic back pain	1.50 (1.29–1.75)	2.39 (2.15–2.64)	4.65 (4.20–5.15)
Work-related musculoskeletal disorder	0.97 (0.66–1.42)	1.98 (1.56–2.50)	2.80 (2.10–3.72)
Chronic lung disease	1.74 (1.29–2.33)	3.91 (3.02–5.07)	5.21 (3.57–7.59)
Cancer	1.20 (0.89–1.63)	2.60 (1.91–3.53)	3.59 (2.65–4.87)
Chronic kidney disease	1.98 (1.44–2.73)	2.20 (1.52–3.21)	3.72 (2.58–5.36)

MDD: major depressive disorder; PR: prevalence ratio. Bold values are statistically significant. [a]Prevalence ratio adjusted for gender and age (reference category: does not have the disease); *95%CI: 95% confidence interval.

of chronic diseases, as well as a strong association between multimorbidity and MDD. Likewise, PRs were higher among men. We also detected a statistically significant interaction between males and multimorbidity, with PR=1.42 (95%CI 1.17–1.73). Interaction data were not shown in the tables.

DISCUSSION

This study revealed that adults (18–59 years) with a self-reported diagnosis of any NCD had a higher prevalence of MDD than individuals without these diseases. The prevalence of MDD also increased with the number of NCDs and the degree of limitation caused by the diseases in the performance of routine activities, both in the general population and in each gender. For almost all diseases evaluated, the prevalence of MDD was significantly higher in women; nevertheless, the relationship between depression and NCDs, expressed by adjusted PRs, tended to be stronger in men. Men also showed an increase of 42% in the association between MDD and multimorbidity, as well as a higher association between MDD and specific morbidities, such as heart disease, arthritis or rheumatism, and chronic

Table 3. Prevalence and prevalence ratio of major depressive disorder according to the presence of chronic diseases in Brazilian male adults (18–59 years). National Health Survey, 2019 (n=31,469).

Chronic diseases	n*	Prevalence of MDD (95%CI)**	PR[a] of MDD (95%CI)**
Hypertension	4,488	9.7 (8.4–11.3)	1.79 (1.49–2.16)
Diabetes	1,208	14.0 (10.9–17.8)	2.37 (1.80–3.11)
Heart disease	810	18.2 (13.7–23.7)	3.11 (2.32–4.15)
Cerebrovascular accident	297	21.7 (15.2–30.0)	3.43 (2.41–4.89)
Asthma or asthmatic bronchitis	1,260	11.0 (8.1–14.7)	1.95 (1.43–2.66)
Arthritis or rheumatism	816	19.8 (14.5–26.3)	3.43 (2.52–4.68)
Chronic back pain	5,386	11.7 (10.2–13.4)	2.43 (2.04–2.89)
Work-related musculoskeletal disorder	478	10.5 (7.2–15.1)	1.74 (1.19–2.55)
Chronic lung disease	273	13.9 (8.9–21.1)	2.33 (1.50–3.63)
Cancer	254	14.1 (8.7–22.0)	2.22 (1.37–3.58)
Chronic kidney disease	332	20.3 (13.2–30.0)	3.44 (2.26–5.23)
Number of chronic diseases			
0	20,241	3.9 (3.4–4.5)	1
1	8,032	7.1 (6.2–8.1)	1.95 (1.60–2.38)
2	2,346	12.8 (10.5–15.5)	3.72 (2.90–4.79)
3	611	21.2 (16.0–27.5)	6.25 (4.53–8.63)
4 or +	239	36.1 (26.2–47.4)	11.19 (7.86–15.92)
Multimorbidityb	3,196	16.1 (13.9–18.6)	4.65 (3.74–5.78)

MDD: major depressive disorder; PR: prevalence ratio. Bold values are statistically significant. *Number of individuals in the non-weighted sample; **95% confidence interval; [a]prevalence ratio adjusted for age (reference category: does not have the disease); [b]≥2 chronic diseases.

Table 4. Prevalence and prevalence ratio of major depressive disorder according to the presence of chronic diseases in Brazilian female adults (18–59 years). National Health Survey, 2019. (n=34,334).

Chronic diseases	n*	Prevalence of MDD (95%CI)**	PR[a] of MDD (95%CI)**
Hypertension	6,903	21.9 (20.3–23.6)	1.61 (1.46–1.78)
Diabetes	1,845	27.3 (23.5–31.5)	1.84 (1.57–2.14)
Heart disease	1,177	31.3 (27.0–36.0)	2.08 (1.78–2.43)
Cerebrovascular accident	406	40.1 (30.7–50.1)	2.58 (1.99–3.35)
Asthma or asthmatic bronchitis	2,051	27.3 (23.9–31.1)	1.88 (1.64–2.16)
Arthritis or rheumatism	2,358	30.0 (26.9–33.2)	2.10 (1.86–2.38)
Chronic back pain	7,026	28.1 (26.4–29.9)	2.39 (2.19–2.60)
Work-related musculoskeletal disorder	872	26.1 (21.9–30.8)	1.70 (1.42–2.04)
Chronic lung disease	398	44.8 (35.0–55.0)	2.98 (2.37–3.74)
Cancer	640	28.2 (22.8–34.4)	1.81 (1.47–2.23)
Chronic kidney disease	419	30.3 (24.0–37.5)	1.95 (1.55–2.44)
Number of chronic diseases			
0	19,123	9.8 (9.0–10.7)	1
1	9,391	17.7 (16.3–19.1)	1.92 (1.71–2.15)
2	3,729	24.0 (21.9–26.3)	2.78 (2.44–3.17)
3	1,408	32.7 (28.4–37.4)	3.98 (3.35–4.72)
4 or +	683	50.0 (42.9–57.1)	6.11 (5.23–7.14)
Multimorbidityb	5,820	29.3 (27.4–31.3)	3.41 (3.05–3.80)

MDD: major depressive disorder; PR: prevalence ratio. Bold values are statistically significant. *Number of individuals in the non-weighted sample; **95% confidence interval; [a]prevalence ratio adjusted for age (reference category: does not have the disease); [b]≥2 chronic diseases.

kidney disease (53, 69, and 79%, respectively). Such interactions reflect a differential effect on MDD from the relationship between the male gender and NCDs.

Despite the methodological differences of the studies regarding instruments and criteria for identifying the presence of depression, the age group assessed, the follow-up duration, the disease severity, and controlled covariates, among other aspects, there is strong evidence of the association between depression and NCDs, with temporal bidirectionality. Namely, the previous history of chronic diseases has been associated with a higher probability of depression[14-16], in the same way that depression has been associated with the incidence of several NCDs[23-29].

In the temporal direction in which depression was posterior to the presence of diseases, studies such as those by Hasan et al.[14] and Chireh et al.[30] revealed a significantly higher risk of individuals with diabetes developing depression (relative risk — RR=1.27; odds ratio — OR 1.33; respectively). In a study based on ten cohorts, ischemic heart disease (IHD) was associated with a higher risk of developing depression, with a hazard ratio (HR) of 1.79 (95%CI 1.43–2.23). The study also estimated the mean time between being diagnosed with IHD and subsequently developing depression in 4.7 years[16]. In a meta-analysis carried out by Xue et al.[15], patients with arthritis were 1.42 times more likely to develop incident depression (95%CI 1.34–1.52) than those without the disease.

On the other hand, studies assessing depression as a risk factor for the incidence of NCDs also provide consistent findings. A meta-analysis based on 11 prospective studies revealed a relative risk of developing hypertension of 1.42 (95%CI 1.09–1.86) among people with depression compared to those without depression[24]. Other investigations also point to depression as a marker of prospective risk for heart disease[25,27,29]. The meta-analysis conducted by Dong et al.[31] showed that people with depression had an increase of 34% (95%CI 17–54) in the risk of developing CVA compared to those without depression, while in the study by Wium-Andersen et al.[16], the diagnosis of depression was associated with a higher risk of IHD (HR=1.63; 95%CI 1.36–1.95). Depressed individuals also presented an increased risk of having asthma at the beginning of adulthood (RR=1.43; 95%CI 1.28–1.61)[32] and of developing type 2 diabetes, ranging from 32% in the study by Yu et al.[28] to 38% in the research by Rotella and Mannucci[26]. Less significantly, another meta-analysis suggested a relationship between depression and the general risk of having cancer (RR=1.15; 95%CI 1.09–1.22), with variation in risk according to the type of cancer[33].

Results of the present study as to the association between MDD and the number of NCDs or multimorbidity are also consistent with the evidence found in the literature. A meta-analysis demonstrated an expressive relationship between multimorbidity and depression — individuals with this condition had almost three times the risk of depressive disorder compared to those without NCDs (RR=2.97; 95%CI 2.06–4.27). The study also showed that, with each additional chronic disease, the risk of having a depressive disorder increased by 45% in relation to those without diseases[34]. From another temporal perspective, a meta-analysis of population-based cross-sectional studies (n=190,593 individuals from 43 low- and middle-income countries, recruited by the World Health Survey) revealed that the chance of multimorbidity was higher among people with depressive episodes (OR 3.44; $p<0.0001$) compared to those without depression[35]. These studies reveal the robust relationship between multimorbidity and depressive disorder, as the associations were significant in all age groups, cultures, and scenarios. Besides, regardless of how depression was measured[34] and the level of depression[35], the relationships remained significant. However, this association is so complex that its simple linearity should not be presumed[34]. The current study evidenced, for example, that the degree of limitation in the performance of routine activities caused by diseases is a factor that interferes with the strength of association with MDD. Also, the possibility of other factors influencing this relationship cannot be dismissed, including the severity and complications of diseases and the different combinations between them, which result in higher health care demands[22].

The complexity of the relationship between depression and NCDs has been explained by different genetic, biological, or behavioral mechanisms[36-39]. In a review study based on 24 articles, the main mechanisms listed were:

1. changes in the hypothalamic-pituitary axis, resulting in excessive production of potentially destructive mediators, such as cortisol and cytokines;
2. unhealthy lifestyles;
3. chronic stressful factors in adulthood and adverse events, which can act as precipitants of depression and have important implications for the development of organic diseases, including the triggering of metabolic syndrome[39].

As for gender differences, the current investigation found that women with NCDs or multimorbidity had a higher prevalence of MDD than men with the same conditions. Nonetheless, the data also revealed that, although associations between NCDs and MDD were significant in both genders, they were stronger among men. In addition, we detected a differential effect on MDD due to the relationship between males and specific diseases (heart disease, arthritis or rheumatism, and chronic kidney disease), as well as between males and multimorbidity. The literature also confirms the greater susceptibility of women to depression[8,9]; however, no studies have been found with analyses stratified by gender on the effects resulting from the interaction between gender and NCDs on mental health. What we observed was research that sought to understand how the interaction between gender and psychological factors impacted the incidence of NCDs or correlated markers[17,18]. From this perspective, Smaardijk et al.[17], in a systematic review and meta-analysis, found that psychological factors were associated with IHD in women (HR=1.22; 95%CI 1.14–1.30) and men (HR=1.25; 95%CI 1.19–1.31), but with no difference between genders (p=0.547). Another meta-analysis showed that, in individuals with IHD, depression was associated with a higher risk of major adverse cardiovascular events (MACE), both in women (HR=1.20; 95%CI 1.10–1.32) and men (HR=1.48; 95%CI 1.32–1.65), with a statistical difference (p=0.005)[18]. Thus, further studies are necessary to clarify the effect of the interaction between gender and NCDs on the association with depression.

Regarding preventive measures, a 2013 PNS study with 60,022 Brazilian adults, using PHQ-9, also identified an association between depression and multimorbidity. Nevertheless, men who practiced the recommended level of physical activity (150 minutes per week) had an attenuation in the association of heart diseases, cancer, and chronic obstructive pulmonary disease (COPD) with depressive symptoms, which reinforces the importance of recommending healthy habits and lifestyles to cope with these conditions[40].

A limitation of this study is its cross-sectional design, which does not allow us to establish causality relationships. The possibility of information bias is another limitation since data were obtained through interviews, and information on the diagnosis of chronic diseases was self-reported. In addition, comparisons with results from other studies were hindered by the use of different sample compositions, instruments, and analysis strategies. However, in order to minimize the effects of such differences, we took the precaution of comparing the results, whenever possible, with systematic reviews and meta-analyses, which identify and summarize the best scientific evidence. We underline that, in all of them, the adult population was included in the analyses.

On the other hand, this study analyzed a representative sample of the Brazilian adult population, which allowed investigating rarer events, and data were collected in a standardized and supervised manner, adopting a validated and widely used instrument to identify the presence of MDD (PHQ-9). This research filled a gap by analyzing the association of MDD with NCDs and multimorbidity, examining the modifying role of gender in these associations. Results of the present investigation raise the hypothesis that the effect of multimorbidity and certain NCDs may be greater on the mental health of men and instigate new studies on the subject.

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