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Multimorbidity in Brazilian adults: magnitude, patterns, individual and state-level inequalities

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Title page

Title: Multimorbidity in Brazilian adults: magnitude, patterns, individual and state-level inequalities

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Abstract

Objectives: Multimorbidity is a public health problem worldwide. In Low and Middle Income Countries (LMIC), such as Brazil, the problem is made worse by greater individual and contextual inequalities. However, little information is available about the topic.

Methods: A national-based cross-sectional study was carried out in 2013 with Brazilian adults. Multimorbidity was evaluated by a list of 22 physical and mental morbidities (based on self-reported medical diagnosis and Patient Health Questionnaire 9 for depression). The outcome was analyzed taking ≥2 and ≥3 diseases as cut-off points. Factor analysis (FA) was used to identify disease patterns and multilevel models were used to test association with individual and contextual variables.

Results: The sample was comprised of 60,202 individuals. Multimorbidity frequency was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. In the multilevel adjusted models, females, older people, those living with a partner and having less schooling presented more multiple diseases. No linear association was found according to asset ownership but greater outcome frequency was found in individuals with mid-range asset ownership quintiles. Living in states with higher levels of education and wealthier states was associated with greater multimorbidity. Two patterns of morbidities (cardiometabolic problems and Respiratory/mental/muscle-skeletal disorders) explained 92% of total variance. The relationship of disease patterns with individual and contextual variables was similar to the multimorbidity cut-off associations.

Conclusions: In Brazil, at least 19 million adults had multimorbidity. Frequency is similar to that found in other LMIC. Contextual and individual social inequalities were observed.

Strengths and limitations of this study

- Comprehensive information about multimorbidity is still scarce in Low and Middle Income countries, especially in Brazil
- As far as we are aware, this is among the first information about multimorbidity occurrence, patterns, individual and contextual factors in a sample representative of the whole of Brazil
- Multimorbidity is a challenge to the Brazilian health system due to its high frequency (two in every ten adults had ≥2 diseases and one in every ten had ≥3 diseases, representing at least 19 million Brazilians) and the interplay of individual and contextual characteristics associated with the problem.
- Except for depression, other morbidities were evaluated by self-reporting and we are not able to evaluate the contextual determinants at neighborhood level

Introduction

Multimorbidity is a current and worldwide public health problem mainly due to its high frequency (>60% in adults) and its association with negative outcomes [1-4]. Most evidence is from High Income Countries [4] but results from Low and Middle Income Countries (LMIC) are also available and increasing in the literature [5-8], including epidemiological information about multimorbidity in Brazilian cities [9-11].

Similar to international evidence, multimorbidity in Brazil is greater in females and increases according to age. Socioeconomic inequalities are also observed mainly related to educational differences whereas multiple disease is more frequent in adults with less schooling and the elderly[10, 11].

However, as far as we are aware, Brazilian evidence on multimorbidity for the entire country is not available. Brazil is the 5th most populous country in the world with more than 200 million people. Furthermore, it is marked by historic social inequalities in different health aspects comprising the occurrence of chronic diseases including both physical and mental disorders [12-14]. Understanding the occurrence and patterns of multimorbidity in the whole country can be relevant for Brazilian Unified Health System management of the challenges resulting from the rapid demographic and epidemiological transitions that have occurred in recent years. Additionally, identifying and comprehending the contextual and individual differences surrounding multimorbidity occurrence helps policy-makers to prioritize and promote health actions and interventions related to multimorbidity management.

Thus, the aim of this study was to evaluate the frequency and patterns of multimorbidity in Brazilian adults, as well to measure their association with individual and contextual factors.

Methods

This was a cross-sectional study using population-based data from the Brazilian National Health Survey (*Pesquisa Nacional de Saúde - PNS)* carried out in Brazil in 2013. The survey was conducted by *Instituto Brasileiro de Geografia e Estatística (IBGE)* and the Ministry of Health. The sample is representative of people living in permanent housing, located in urban or rural areas, covering the country's five major geographical regions, its 26 states and Federal District.

Sampling was done in three stages, the first being the selection of census tracts, followed by households and, finally, individuals aged 18 or over. More details about the sampling process can be found elsewhere[15, 16].

Multimorbidity was evaluated by using a list of all 22 self-reported morbidities available in the study, 21 of which were based on self-reported medical diagnosis, while depression was based on the Patient Health Questionnaire-9(PHQ-9)[17]. The question applied to measure each disease based on self-reported medical diagnosis was: *"Has any physician already diagnosed you as having [each disease]?"*.The following morbidities were included: High Blood Pressure - HBP; Spinal column problem; Hypercholesterolemia; Depression; Diabetes; Arthritis/rheumatism; Asthma/wheezy bronchitis; Work-related muscle-skeletal disorders; Cancer; Other heart disease; Stroke; Kidney problem; Heart attack; Heart failure; Bronchitis; Angina; Emphysema; Other lung disease; Bipolar disorder; Other mental disease; Schizophrenia; and Obsessive Compulsive Disorder (OCD). Multimorbidity was evaluated by two cut-off points as per the literature[4, 18]: ≥2and ≥3morbidities. Women who had HBP or diabetes only during pregnancy were considered as not having these diseases.

Independent variables were sex (male; female), age (continuous), Skin color (white; black; and brown - Asian-Brazilian and indigenous were not shown because they represented less than 1.6% of the sample), marital status (without partner; with partner), schooling in years (0: No schooling; 1-8: incomplete primary school; 8-11: complete primary school and incomplete secondary school; ≥12: complete secondary school up to complete higher education), asset ownership in quintiles (based on ownership of bathroom, car, motorcycle, refrigerator, washing machine, DVD player, TV, landline telephone, microcomputer and microwave oven), private health plan (no; yes), geographical area (urban; rural); state-level education in terciles – proportion of literacy rate obtained from IBGE, 2010 and state-level income in terciles (nominal income per capita - average monthly value - in permanent private housing obtained from IBGE, 2010).

Statistical analyses were performed using Stata 12.1 software and the *svy* command was used, which takes into consideration sample weights. Sample weights were defined for the primary sampling units, households and all inhabitants, as well as for the selected inhabitant. Complete information about PNS sample weights and sampling process have been published elsewhere [15, 16]. The results from the sample were expanded for the Brazilian population.

Descriptive analysis was based on the calculation of prevalence and its respective confidence intervals. Factor analysis (FA) was performed to identify patterns of morbidities[19]. This analysis was based on tetrachoric correlation, this being more appropriate than Pearson's correlation for dichotomous variables [20]. Before FA analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett sphericity tests were used to evaluate the applicability of this approach. After the first evaluation of the model, some variables were excluded (bronchitis, emphysema, other lung disease, other mental disease and other heart disease) in order to obtain a better model fit. Oblique (oblimin or promax) rotation was performed. In order to establish the number of

components to be retained, we used Cattel graphics, Kaiser criteria (eigenvalue>1) and minimum explained variance (>10% for each component). Variables with loadings |≥0.3| were kept [21]. Through factorial analysis, we obtained the predicted scores of morbidities (factors).

Multilevel models were performed to account for state-level variance, with the individuals as the first level and the state of residence as the second level. First, the models were initially adjusted without inclusion of the independent variables (null model) to test the initial variance attributable to the state accounting for approximately 1% ($p<0.05$) of variance for the four analyses (Multimorbidity ≥2; Multimorbidity ≥3, factor 1 and factor 2). Then, we performed a logistic regression model for multimorbidity (≥2 and ≥3 morbidities) and linear regression models to evaluate the association of factors (patterns) of diseases and independent variables. We included sex, age, skin color, marital status, schooling in years, private health plan, geographical area, state-level education and income in these models.

Results

The sample was comprised of 60,202 adults. The most frequent diseases were High Blood Pressure (22.3%) and Spinal column problem (19.0%). Angina, emphysema, other lung disease, bipolar disorder, other mental disease, schizophrenia and Obsessive Compulsive Disorder (OCD) were present in less than 1% of the sample. Lung disease problems showed, on average, longer duration of disease. Greater comorbidities were observed for individuals with health problems (heart attack; heart failure and angina). The mean range of comorbidities was from 2.3 to 4.5 diseases (Table 1).

Females comprised 55.1% of the sample and mean age was 43.7 years (SD=17.0), ranging from 18 to 101. Most individuals reported white skin color (47.8%) followed by brown (41.7%). Almost two thirds lived with a partner. Out of the total sample, 45.2% had ≥12 years of schooling and 13.9% had zero schooling. Less than one third had a private health plan and 13.5% lived in rural areas (Table 2). The mean average proportion of literacy rate at the state-level was 7.3%, ranging from 3.3% to 22.5%. The average monthly value of nominal income per capita was R$ 1,069 (approximately US$ 644 in 2010).

The occurrence of multimorbidity was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. Irrespective of cut-off point, multimorbidity was higher in females, older people, individuals reporting white skin color, who lived with a partner, had less schooling, had a private health plan and living in urban areas. At state-level, multimorbidity was more frequent in states with higher education levels and wealthier states (Table 2).

In the adjusted multilevel models, females had 1.86 (CI95% 1.78; 1.95) and 1.97(CI95% 1.85; 2.10) more odds of multimorbidity than males, for ≥2 and ≥3 morbidities, respectively.

In all cases, every additional year of age increased by 1.06 times the odds of multiples diseases. Self-reported skin color was not associated with multimorbidity in the adjusted models. On average, living with a partner increased by 1.15 times the odds of the outcome. Compared to individuals with ≥12 years of schooling, adults with 1-8 years of schooling had more odds of multimorbidity (OR 1.40 - CI95% 1.32; 1.49, for ≥2 diseases and OR 1.58 CI95% 1.45; 1.72, for ≥3 morbidities). In general, adults in the second and third wealthiest quintiles had greater odds of multimorbidity. Individuals with private health plans and who lived in urban areas had greater odds of multiple diseases. Individuals who lived in states with low and middle education levels had less multimorbidity compared to states with high education levels. With regard to income at state-level, the higher multimorbidity difference was demonstrated simply by comparing low with high income states (Table 3).

In the FA analysis, the KMO coefficient was 0.84. Two patterns of morbidities explained 92% of total variance, after rotation. The two components identified were: (1) cardiometabolic problems (High Blood Pressure, heart attack, angina, heart failure, stroke, hypercholesterolemia, diabetes and arthritis/rheumatism); (2) Respiratory/mental/muscle-skeletal disorders (arthritis/rheumatism, spinal column problem, asthma/wheezy bronchitis, COPD, work-related muscle-skeletal disorders, depression, bipolar disorder and kidney problem) (Table4).

The adjusted multilevel analyses of the two factors are presented in Table 5. Overall, the results were similar to those observed in Table 3. Females, older people, those with less schooling, those with intermediate asset ownership quintiles and who had private health plans showed more burden of factors. People who lived in rural geographical areas showed less burden of the cardiometabolic factor. Individuals with partners presented less burden of the Respiratory/mental/muscle-skeletal factor compared to individuals who did not have a

partner. Cardiometabolic and Respiratory/mental/muscle-skeletal factors were greater when state-level education and income were lower.

Discussion

Multimorbidity frequency in Brazil is considerable; one in every five Brazilian adults had two or more morbidities and one in every ten had three or more morbidities. Individual and state-level inequalities suggest the complexity of factors and their relationship with multimorbidity occurrence. To our knowledge, this is the first representative Brazilian study to consider individual and contextual factors associated with multimorbidity and its clusters.

The study's national representativeness enables us to extrapolate frequencies for the whole Brazilian adult population. Considering 190,755,799 million adults in the most recent Brazilian population census (2010), we are able to infer that approximately 42.7 and 19.5 million Brazilian adults had two or more and three or more diseases, respectively. These results bring important challenges for the health system which will need to be more comprehensive in order to deal with the complexity of multimorbidity. Some of the issues are related to need to include multimorbidity in guidelines on reporting these problems to health professionals, as well as giving more emphasis to multimorbidity on health-related university curricula.

Relative comparisons with Western countries reveal similar occurrence of two or more diseases in Spain[22] (20.0%; CI95%: 18.8-21.2) and almost ten percentage points less than in Scotland [23] (31.1%, 25 or more years) and Canada[24] (30.9%; CI95% 29.5 – 32.4).In low and middle income countries (LMIC), estimates from countries (China, Ghana, India, Mexico, Russia, and South Africa) included in the WHO Study on global AGEing and adult health (SAGE) Wave-1 (2007/10), found 21.9% (CI95%: 20.9; 22.9) of multimorbidity occurrence (≥2 diseases from a list from eight morbidities)[5]. This occurrence varied from 20.3% in China to 34.7% in Russia. In the present analysis, we used more diseases to

construct multimorbidity (22 against eight in SAGE study). Even so, the prevalence found was, virtually, equal to these other LMIC countries, except for Russia.

In Brazil, our occurrence findings were lower than frequencies found in a Southern Brazilian city (29.1%; CI95%: 27.1; 31.1 for ≥2 morbidities, and 14.3 %; CI95%: 12.8; 15.8 for ≥3 morbidities) despite the higher number of morbidities included in this study [10]. The difference observed may be attributed to socioeconomic characteristics of Brazilian states. The Southern states presented more income and schooling which tend to increase the burden of multimorbidity as observed in the results presented here.

In terms of socio-demographic characteristics, females and older adults presented more multimorbidity as found in previous Brazilian [10, 11] and international studies [25, 26]. Women tend to use health services more and to live longer than males, these being factors which explain part of the higher frequency in this group. Older adults show more exposure to events, including unhealthy ones, that contribute to chronic disease incidence. In the same way, individuals who had partners had higher multimorbidity.

Regarding socioeconomic variables, our results follow the pattern found in overall analysis of LMIC included in the SAGE study. Multimorbidity was not associated with wealth quintiles but presented association with education [5]. In the present analysis, the middle wealth quintile strata and their clusters present more multimorbidity whilst showing a negative dose-response relationship with education. These results may be explained by a strong relationship between educational attainment and all aspects of healthier life including those mainly related to better awareness of chronic disease risk factors [27, 28].

Having private health plans was associated with multimorbidity and its factors. This may be explained by role of health plans as a socioeconomic indicator but, even more so, by the

relationship with self-reported diagnosis (used here to construct the outcome). Individuals with health plans tend to use health services more frequently regardless the presence of chronic conditions[29, 30] thus affording more diagnosis.

Individuals who lived in urban areas presented more multiple diseases. This was similar to results found in the adult population in South Africa [31] and Catalonia (Spain)[32]. In spite of little Brazilian evidence on the topic, as well as the social, cultural and environment differences between rural-urban residents, people from rural areas had more difficulty in accessing health services in Brazil [33]which may explain partially the differences between rural and urban residents in our results of the occurrence of self-reported medical diagnosis of multiple diseases.

The state-level differences observed reveal a paradoxical association. Instead of individual inequalities are pro-rich, state-level differences are pro-poor. These results might be explained by demographic differences between states in Brazil which may not be fully adjusted with individual demographic variables included in the analysis. Low income and low education in Brazilian states are concentrated in North and Northeast regions and show the poorest health-related indicators[12].

The two factors (cardiometabolic and respiratory/mental/muscle-skeletal) found have some similarity to recent evidence [34, 35] mainly related to cardiometabolic patterns. The respiratory/mental/muscle-skeletal data found was similar to results found in a worldwide study of people aged 50 or over [36]. The majority of studies, especially with adult populations, found two or three patterns of diseases. These combinations of diseases suggest possible causal relationship between diseases or their risk factors [19]. The cardiometabolic pattern showed a more well know relationship between diseases. On the other hand, the

relationship between respiratory, mental and muscle-skeletal disorders is less understood. The concomitant occurrence of these diseases is well described [37] but understanding the biological plausibility of causal relationships will be a challenge for new studies. As a first step, more detailed and specific information about onset of diseases will be needed. At the same time, the use of approaches related to network analysis can be useful for a better understanding of causal relationships [38]. Even so, the results presented here may contribute to the inclusion of recommendations in Brazilian clinical guidelines about the relationship with chronic conditions, as well as to designing interventions/public policies considering the presence of multiple diseases in the same individual.

Some limitations of the study should be addressed. With the exception of depression, all the other morbidities were evaluated by self-reporting. This may provide a misclassification bias even though self-reported diagnosis is considered an adequate and common source of information used in population-based studies on multimorbidity [4, 39, 40]. Nevertheless, the lack of adequate information about diagnosis, including longitudinal information, limits the causal inference related to concomitant diseases expressed in factorial analysis. Furthermore, we are not able to evaluate the contextual determinants at neighborhood level which may produce more complete associations with state-level differences.

The absolute and relative number of Brazilian individuals with multimorbidity was high. Addressing the complexity of multiple disease management for at least 19 million people will be a challenge for the health system. The clusters of diseases identified might contribute to strategies for the prevention and clinical care of these diseases. State-level and individual inequalities increase the problem reinforcing the need of a wide lens to organize health services and to decrease the inequities among the Brazilian population.

Author contributions

BPN designed the article, obtained and analyzes the data, drafted the first version and revised the manuscript. ADPCF and FACF analyzed the data, and drafted and revised the manuscript. SP, DS, TRF, TNM, ET and LAF drafted and revised the manuscript. SBR designed the article, drafted and revised the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest: All authors have no potential conflicts.

Data sharing statement: All PNS data are available from the Brazilian Institute of Geography and Statistics website, located here: http://www.ibge.gov.br/home/estatistica/populacao/pns/2013/default_microdados.shtm.

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Tables and figures

Table 1. Individual prevalence, duration and number of comorbidities for each morbidity evaluated. Brazil, 2013.

Morbidities	Individual prevalence		Duration of disease	Number of comorbidities
	%	(95%CI)	Mean (median; Q25-Q75)	Mean (median; Q25-Q75)
High Blood Pressure	22.3	21.7 - 23.0	13.1 (9; 3-18)	2.3 (2; 1-3)
Spinal column problem	19.0	18.3 - 19.7	14.7 (10; 4-21)	2.3 (2; 1-3)
Hypercholesterolemia	8.4	8.0 - 8.8	6.9 (3; 1-9)	2.3 (2; 1-3)
Arthritis/rheumatism	6.7	6.4 - 7.1	14.6 (10; 3-20)	3.0 (3; 2-4)
Diabetes	6.5	6.2 - 6.9	11.3 (6; 2-15)	2.9 (3; 2-4)
Asthma/wheezy bronchitis	4.4	4.1 - 4.8	25.1 (23; 13-35)	2.4 (2; 1-3)
Depression	4.2	3.9 - 4.5	-	2.9 (3; 2-4)
Work-related muscle-skeletal disorders	2.5	2.2 - 2.8	7.5 (5; 2-11)	2.5 (2; 1-3)
Cancer	1.9	1.7 - 2.2	8.5 (6; 2-13)	2.8 (2; 2-4)
Another heart disease	1.9	1.6 - 2.1	13.9 (9; 3-20)	3.1 (3; 2-4)
Stroke	1.6	1.4 - 1.8	10.2 (6; 2-13)	3.4 (3; 2-5)
Kidney problem	1.5	1.3 - 1.7	13.5 (9; 3-20)	3.2 (3; 2-4)
Heart attack	1.3	1.2 - 1.5	12.4 (7; 2-18)	4.0 (4; 3-5)
Heart failure	1.2	1.1 - 1.4	13.2 (8; 4-19)	4.0 (4; 2-5)
Bronchitis	1.0	0.8 - 1.1	23.2 (20; 9-32)	3.3 (3; 2-5)
Angina	0.8	0.7 - 0.9	15.5 (11; 5-21)	4.5 (4; 3-6)
Emphysema	0.5	0.4 - 0.6	14.9 (9; 3-18)	3.7 (3; 2-5)
Another lung disease	0.5	0.4 - 0.6	16.2 (12; 5-24)	2.8 (2; 1-4)
Bipolar disorder	0.4	0.3 - 0.5	11.3 (8; 4-16)	3.1 (3; 2-4)
Another mental disease	0.3	0.2 - 0.4	2.8 (2; 1-4)	2.5 (2; 1-3)
Schizophrenia	0.2	0.2 - 0.3	19.7 (19; 8-26)	2.7 (3; 2-3)
Obsessive Compulsive Disorder (OCD)	0.2	0.1 - 0.2	14.5 (12; 6-21)	3.4 (3; 2-4)

406 Table 2. Description of the sample and multimorbidity frequency. Brazil, 2013.

Variables	n	%	Multimorbidity ≥2 %	95%CI	≥3 %	95%CI
Sex						
Male	25,920	44.9	17.5	16.6; 18.3	7.2	6.6; 7.8
Female	34,282	55.1	26.1	25.2; 27.0	12.6	12.0; 13.3
Age (in years)						
18 to 29	14,321	24.3	4.9	4.2; 5.6	1.2	0.9; 1.5
30 to 39	14,269	21.0	10.6	9.6; 11.5	2.8	2.3; 3.3
40 to 49	11,405	18.8	20.8	19.5; 22.1	7.8	7.0; 8.6
50 to 59	9,030	16.8	32.9	31.2; 34.6	15.5	14.3; 16.8
60 to 69	6,238	10.8	46.3	44.1; 48.6	24.7	22.8; 26.6
70 to 79	3,441	5.7	52.2	49.2; 55.2	30.9	28.0; 33.9
80 or more	1,498	2.6	52.8	48.6; 57.0	30.6	26.5; 34.7
Skin color*						
White	24,106	47.8	24.3	23.3; 25.4	11.6	10.8; 12.3
Black	5,631	9.2	22.2	20.2; 24.2	10.3	8.9; 11.6
Brown	29,512	41.7	19.8	18.9; 20.6	8.6	8.1; 9.2
Marital status						
Without partner	25,680	38.4	20.6	19.7; 21.5	9.9	9.3; 10.6
With partner	34,522	61.6	23.2	22.4; 24.1	10.4	9.7; 11.0
Schooling (in years)						
0	9,434	13.9	33.2	31.4; 35.0	16.3	14.9; 17.7
1-8	14,649	25.7	30.0	28.6; 31.4	16.1	14.9; 17.2
8-11	9,215	15.3	17.9	16.5; 19.3	7.5	6.5; 8.4
≥12	26,904	45.2	15.8	15.0; 16.7	5.9	5.4; 6.5
Asset ownership (in quintiles)						
1º (High)	10,153	22.3	22.0	20.5; 23.6	9.3	8.3; 10.4
2º	11,531	22.4	22.3	21.0; 23.6	10.5	9.5; 11.5
3º	11,621	19.5	23.1	21.8; 24.4	10.6	9.7; 11.5
4º	14,380	21.0	22.2	20.9; 23.5	10.6	9.7; 11.6
5º (Low)	12,517	14.7	21.3	19.9; 22.7	9.9	8.9; 10.9
Private health plan						
No	43,834	69.4	21.1	20.3; 21.9	9.8	9.3; 10.4
Yes	16,368	30.6	24.8	23.5; 26.1	11.0	10.1; 12.0
Geographical area						
Urban	49,245	86.5	22.8	22.0; 23.5	10.5	10.0; 11.1
Rural	10,957	13.5	18.6	17.2; 20.0	8.0	7.1; 8.8
State-level education						
High	22,382	37.2	24.7	23.7; 25.7	11.7	10.9; 12.4
Middle	19,515	32.4	20.1	18.6; 21.7	9.3	8.3; 10.4

Low	18,305	30.4	19.0	18.0; 20.1	8.0	7.3; 8.6
State-level income						
High	21,683	36.0	24.6	23.6; 25.7	11.6	10.8; 12.3
Middle	18,087	30.0	21.8	20.2; 23.3	10.5	9.5; 11.6
Low	20,432	33.9	18.2	17.2; 19.2	7.5	6.9; 8.1
Total	60,202	100.0	22.2	21.5; 22.9	10.2	9.7; 10.7

Table 3. Adjusted multilevel models of multimorbidity with independent variables. Brazil, 2013.

Variables	Multimorbidity (≥2)						Multimorbidity (≥3)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%
Sex (ref: male)												
Female	**1.84**	**1.76; 1.94**	**1.85**	**1.77; 1.94**	**1.85**	**1.77; 1.94**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.09**
Age (in years)	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**
Skin color* (ref: White)												
Black	1.07	0.99; 1.16	1.08	0.99; 1.17	1.08	0.99; 1.17	1.09	0.98; 1.21	1.09	0.98; 1.21	1.09	0.98; 1.21
Brown	1.01	0.96; 1.06	1.01	0.96; 1.07	1.01	0.96; 1.07	0.97	0.91; 1.04	0.97	0.91; 1.04	0.97	0.91; 1.04
Marital status (ref: Without partner)												
With partner	**1.13**	**1.08; 1.18**	**1.13**	**1.08; 1.19**	**1.13**	**1.08; 1.19**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**
Schooling (in years) [#] (ref: ≥12)												
8-11	**1.19**	**1.11; 1.28**	**1.19**	**1.10; 1.28**	**1.19**	**1.10; 1.28**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**
1-8	**1.41**	**1.33; 1.51**	**1.41**	**1.33; 1.50**	**1.41**	**1.33; 1.50**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**
0	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.41**	**1.27; 1.56**	**1.41**	**1.28; 1.56**	**1.41**	**1.28; 1.56**
Asset ownership (in quintiles) (ref: High)												
2º	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**
3º	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**
4º	1.05	0.96; 1.14	1.05	0.97; 1.14	1.05	0.97; 1.14	1.09	0.98; 1.22	1.10	0.98; 1.23	1.10	0.98; 1.23
5º (Low)	0.91	0.83; 1.00	0.92	0.84; 1.01	0.92	0.84; 1.01	0.95	0.84; 1.08	0.95	0.84; 1.08	0.95	0.84; 1.08
Private health plan (ref: no)												
Yes	**1.15**	**1.08; 1.21**	**1.15**	**1.08; 1.20**	**1.15**	**1.08; 1.20**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**
Geographical area (ref: urban)												
Rural	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**
State-level education (ref: High)												
Middle			**0.82**	**0.71; 0.94**					**0.76**	**0.64; 0.90**		
Low			**0.83**	**0.72; 0.96**					**0.76**	**0.64; 0.90**		
State-level income (ref: High)												
Middle					0.89	0.77; 1.04					0.88	0.73; 1.05
Low					**0.82**	**0.71; 0.95**					**0.75**	**0.63; 0.89**

Table 4. Factor analysis. Brazil, 2013.

Morbidities	Factor 1	Factor 2
High Blood Pressure	0.77	
Heart attack	0.79	
Angina	0.68	
Heart failure	0.69	
Stroke	0.58	
Hypercholesterolemia	0.57	
Diabetes	0.62	
Arthritis/rheumatism	0.30	0.37
Spinal column problem		0.45
Asthma/wheezy bronchitis		0.57
COPD		0.63
Work-related muscle-skeletal disorders		0.45
Depression		0.46
Bipolar disorder		0.46
Kidney problem		0.31
Cancer	-	-
Eigenvalor	4.46	1.11
Explained variance %*	0.73 (0.69)	0.18 (0.47)
KMO	0.84	

*Before oblique rotation (after oblique rotation)

411 Table 5. Adjusted multilevel models of patterns of diseases (factors) with independent variables. Brazil, 2013.

Variables	Factor 1 (Cardiometabolic)						Factor 2 (Respiratory/mental/ muscle-skeletal)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%
Sex (ref: male)												
Female	**.024**	**.022; .026**	**.024**	**.022; .026**	**.024**	**.022; .026**	**.038**	**.036; .040**	**.038**	**.036; .040**	**.038**	**.036; .040**
Age (in years)	**.004**	**.004; .004**	**.004**	**.004; .004**	**.004**	**.004; .004**	**.001**	**.001; .001**	**.001**	**.001; .001**	**.001**	**.001; .001**
Skin color* (ref: White)												
Black	**.007**	**.003; .010**	**.007**	**.003; .010**	**.007**	**.003; .010**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**
Brown	.001	-.001; .004	.002	-.001; .004	.002	-.001; .004	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**
Marital status (ref: Without partner)												
With partner	.000	-.002; .002	.000	-.002; .002	.000	-.002; .002	**-.005**	**-.007; -.002**	**-.005**	**-.007; -.003**	**-.005**	**-.007; -.003**
Schooling (in years) [#] (ref: ≥12)												
8-11	**.013**	**.010; .016**	**.013**	**.010; .016**	**.013**	**.010; .016**	**.004**	**.001; .008**	**.005**	**.002; .008**	**.005**	**.002; .008**
1-8	**.021**	**.018; .023**	**.021**	**.018; .023**	**.021**	**.018; .023**	**.011**	**.008; .014**	**.011**	**.008; .014**	**.011**	**.008; .014**
0	**.014**	**.010; .017**	**.014**	**.010; .017**	**.014**	**.010; .017**	.001	-.003; .004	.001	-.003; .005	.001	-.003; .005
Asset ownership (in quintiles) (ref: High)												
2º	**.007**	**.004; .010**	**.007**	**.004; .010**	**.007**	**.004; .010**	**.005**	**.001; .008**	**.005**	**.001; .008**	**.005**	**.001; .008**
3º	**.009**	**.006; .013**	**.009**	**.006; .013**	**.009**	**.006; .013**	**.010**	**.006; .014**	**.010**	**.006; .014**	**.010**	**.006; .014**
4º	**.006**	**.002; .009**	**.006**	**.002; .009**	**.006**	**.002; .009**	.004	.000; .008	.004	.000; .008	.004	.000; .008
5º (Low)	-.003	-.007; .001	-.003	-.007; .001	-.003	-.007; .001	.001	-.004; .005	.001	-.004; .005	.001	-.004; .005
Private health plan (ref: no)												
Yes	**.006**	**.004; .009**	**.006**	**.004; .009**	**.006**	**.004; .009**	**.007**	**.005; .010**	**.007**	**.005; .010**	**.007**	**.005; .010**
Geographical area (ref: urban)												
Rural	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	-.002	-.005; .002	-.002	-.005; .002	-.002	-.005; .002
State-level education (ref: High)												
Middle			**-.010**	**-.016; -.004**					**-.016**	**-.027; -.005**		
Low			**-.008**	**-.015; -.002**					**-.018**	**-.029; -.006**		
State-level income (ref: High)												
Middle					-.006	-.012; .001					-.011	-.022; .001
Low					**-.009**	**-.016; -.003**					**-.017**	**-.028; -.006**

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Contextual and individual inequalities of multimorbidity in Brazilian adults: a cross-sectional national-based study

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Secondary Subject Heading:	Public health
Keywords:	Comorbidity, Multimorbidity, Chronic disease, Statistical disease clustering, Multilevel Analysis

Title page

Title: Contextual and individual inequalities of multimorbidity in Brazilian adults: a cross-sectional national-based study

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Key-words: Comorbidity; Multimorbidity; Chronic disease; Statistical disease clustering; Multilevel Analysis.

Word count: 3094

Abstract

Objectives: The study aims to evaluate the magnitude of multimorbidity in Brazilian adults, as well to measure their association with individual and contextual factors stratified by Brazilian states and regions.

Methods: A national-based cross-sectional study was carried out in 2013 with Brazilian adults. Multimorbidity was evaluated by a list of 22 physical and mental morbidities (based on self-reported medical diagnosis and Patient Health Questionnaire 9 for depression). The outcome was analyzed taking ≥2 and ≥3 diseases as cut-off points. Factor analysis (FA) was used to identify disease patterns and multilevel models were used to test association with individual and contextual variables.

Results: The sample was comprised of 60,202 individuals. Multimorbidity frequency was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. In the multilevel adjusted models, females, older people, those living with a partner and having less schooling presented more multiple diseases. No linear association was found according to asset ownership but greater outcome frequency was found in individuals with mid-range asset ownership quintiles. Living in states with higher levels of education and wealthier states was associated with greater multimorbidity. Two patterns of morbidities (cardiometabolic problems and Respiratory/mental/muscle-skeletal disorders) explained 92% of total variance. The relationship of disease patterns with individual and contextual variables was similar to the overall multimorbidity, with differences among Brazilian regions.

Conclusions: In Brazil, at least 19 million adults had multimorbidity. Frequency is similar to that found in other LMIC. Contextual and individual social inequalities were observed.

Strengths and limitations of this study

- Comprehensive information about multimorbidity is still scarce in Brazil
- As far as we are aware, this is among the first information about multimorbidity assessment of individual and contextual factors in a sample representative of the whole of Brazil
- Multimorbidity is a challenge to the Brazilian health system due to its high frequency (two in every ten adults had ≥2 diseases and one in every ten had ≥3 diseases, representing at least 19 million Brazilians) and the interplay of individual and contextual characteristics associated with the problem. Differences within the country were observed.
- Except for depression, other morbidities were evaluated by self-reporting and we are not able to evaluate the contextual determinants at neighborhood level

Introduction

Multimorbidity is a current and worldwide public health problem mainly due to its high frequency (>60% in adults) and its association with negative outcomes [1-4]. Most evidence is from High Income Countries [4] but results from Low and Middle Income Countries (LMIC) are also available and increasing in the literature [5-8], including epidemiological information about multimorbidity in Brazilian cities [9-11].

Similar to international evidence, multimorbidity in Brazil is greater in females and increases according to age. Socioeconomic inequalities are also observed mainly related to educational differences whereas multiple disease is more frequent in adults and elderly with less schooling and lower socioeconomic status adults and elderly [10 11].

However, as far as we are aware, Brazilian evidence on multimorbidity for the entire country is scarce. Only recently, a paper evaluating epidemiology of multimorbidity in Brazil was published [12]. The authors found a 24.2% (95% CI 23.5–24.9) prevalence rate of multimorbidity [12] and correlates were similar to Brazilian located previous studies ([10 11].

Brazil is the 5th most populous country in the world with more than 200 million people. Furthermore, it is marked by historic social inequalities in different health aspects comprising the occurrence of chronic diseases including both physical and mental disorders [13-15]. Understanding the occurrence and patterns of multimorbidity in the whole country can be relevant for Brazilian Unified Health System management of the challenges resulting from the rapid demographic and epidemiological transitions that have occurred in recent years. Additionally, identifying and comprehending the contextual and individual differences

surrounding multimorbidity occurrence helps policy-makers to prioritize and promote health actions and interventions related to multimorbidity management.

Thus, the aim of this study was to evaluate the frequency and patterns of multimorbidity in Brazilian adults, as well to measure their association with individual and contextual factors stratified by Brazilian states and regions.

Methods

This was a cross-sectional study using population-based data from the Brazilian National Health Survey (*Pesquisa Nacional de Saúde - PNS)* carried out in Brazil in 2013. The survey was conducted by *Instituto Brasileiro de Geografia e Estatística (IBGE)* and the Ministry of Health. The sample is representative of people living in permanent housing, located in urban or rural areas, covering the country's five major geographical regions, its 26 states and Federal District.

Sampling was done in three stages, the first being the selection of census tracts, followed by households and, finally, individuals aged 18 or over. More details about the sampling process can be found elsewhere[16 17].

Multimorbidity was evaluated by using a list of all 22 self-reported morbidities available in the study, 21 of which were based on self-reported medical diagnosis, while depression was based on the Patient Health Questionnaire-9(PHQ-9)[18]. The question applied to measure each disease based on self-reported medical diagnosis was: *"Has any physician already diagnosed you as having [each disease]?"*.The following morbidities were included: High Blood Pressure - HBP; Spinal column problem; Hypercholesterolemia; Depression; Diabetes; Arthritis/rheumatism; Asthma/wheezy bronchitis; Work-related muscle-skeletal disorders; Cancer; Other heart disease; Stroke; Kidney problem; Heart attack; Heart failure; Bronchitis; Angina; Emphysema; Other lung disease; Bipolar disorder; Other mental disease; Schizophrenia; and Obsessive Compulsive Disorder (OCD). Multimorbidity was evaluated by two cut-off points as per the literature[4 19]: ≥2and ≥3morbidities. Women who had HBP or diabetes only during pregnancy were considered as not having these diseases.

Independent variables were sex (male; female), age (continuous), skin color (white; black; and brown - Asian-Brazilian and indigenous were not shown because they represented less than 1.6% of the sample), marital status (without partner; with partner), schooling in years (0: No schooling; 1-8: incomplete primary school; 8-11: complete primary school and incomplete secondary school; ≥12: complete secondary school up to complete higher education), wealth index in quintiles (based on ownership of bathroom, car, motorcycle, refrigerator, washing machine, DVD player, TV, landline telephone, microcomputer and microwave oven), private health plan (no; yes), geographical area (urban; rural); state-level education in terciles – proportion of literacy rate obtained from IBGE, 2010 and state-level income in terciles (nominal income per capita - average monthly value - in permanent private housing obtained from IBGE, 2010).

Statistical analyses were performed using Stata 12.1 software and the *svy* command was used, which takes into consideration sample weights. Sample weights were defined for the primary sampling units, households and all inhabitants, as well as for the selected inhabitant. Complete information about PNS sample weights and sampling process have been published elsewhere [16 17]. The results from the sample were expanded for the Brazilian population.

Descriptive analysis was based on the calculation of prevalence and its respective confidence intervals. Factor analysis (FA) was performed to identify patterns of morbidities[20]. This analysis was based on tetrachoric correlation, this being more appropriate than Pearson's correlation for dichotomous variables [21]. Before FA analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett sphericity tests were used to evaluate the applicability of this approach. After the first evaluation of the model, some variables were encompassed (bronchitis, emphysema and other lung disease to other respiratory problems - COPD) and others excluded (schizophrenia, Obsessive Compulsive Disorder, another mental disease and another heart disease) in order to

obtain a better model fit regarding KMO and Bartlett sphericity tests. Oblique (oblimin or promax) rotation was performed. In order to establish the number of components to be retained, we used Cattel graphics, Kaiser criteria (eigenvalue>1) and minimum explained variance (>10% for each component). Variables with loadings |≥0.3| were kept [22]. Through factorial analysis, we obtained the predicted scores of morbidities (factors).

Multilevel models were performed to account for state-level variance, with the individuals as the first level and the state of residence as the second level. First, the models were initially adjusted without inclusion of the independent variables (null model) to test the initial variance attributable to the state accounting for approximately 1% ($p<0.05$) of variance for the four analyses (Multimorbidity ≥2; Multimorbidity ≥3, factor 1 and factor 2). Then, we performed a logistic regression model for multimorbidity (≥2 and ≥3 morbidities) and linear regression models to evaluate the association of factors (patterns) of diseases and independent variables. We included sex, age, skin color, marital status, schooling in years, private health plan, geographical area, state-level education and income in these models. Stratified region-level analyzes were performed to better understanding disparities among states.

The study was approved by the National Research Ethics Commission on July 8, 2013, under No. 10853812.7.0000.0008. All respondents signed a free and informed consent statement form prior to data collection

Results

The sample was comprised of 60,202 adults. The most frequent diseases were High Blood Pressure (22.3%) and Spinal column problem (19.0%). Angina, emphysema, other lung disease, bipolar disorder, other mental disease, schizophrenia and Obsessive Compulsive Disorder (OCD) were present in less than 1% of the sample. Lung disease problems showed, on average, longer duration of disease. Greater comorbidities were observed for individuals with health problems (heart attack; heart failure and angina). The mean range of comorbidities was from 2.3 to 4.5 diseases (Supplementary table 1).

Females comprised 55.1% of the sample and mean age was 43.7 years (SD=17.0), ranging from 18 to 101. Most individuals reported white skin color (47.8%) followed by brown (41.7%). Almost two thirds lived with a partner. Out of the total sample, 45.2% had ≥12 years of schooling and 13.9% had zero schooling. Less than one third had a private health plan and 13.5% lived in rural areas (Table 1). The mean average proportion of literacy rate at the state-level was 7.3%, ranging from 3.3% to 22.5%. The average monthly value of nominal income per capita was R$ 1,069 (approximately US$ 644 in 2010).

The occurrence of multimorbidity was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. Irrespective of cut-off point, multimorbidity was higher in females, older people, individuals reporting white skin color, who lived with a partner, had less schooling, had a private health plan and living in urban areas. At state-level, multimorbidity was more frequent in states with higher education levels and wealthier states (Table 1). States in the South of Brazil showed the highest occurrence of multimorbidity (Supplementary figure 1),

In the adjusted multilevel models, females had 1.86 (CI95% 1.78; 1.95) and 1.97(CI95% 1.85; 2.10) more odds of multimorbidity than males, for ≥2 and ≥3 morbidities, respectively. In all cases, every additional year of age increased by 1.06 times the odds of multiples diseases. Self-reported skin color was not associated with multimorbidity in the adjusted models. On average, living with a partner increased by 1.15 times the odds of the outcome. Compared to individuals with ≥12 years of schooling, adults with 1-8 years of schooling had more odds of multimorbidity (OR 1.40 - CI95% 1.32; 1.49, for ≥2 diseases and OR 1.58 CI95% 1.45; 1.72, for ≥3 morbidities). In general, adults in the second and third wealthiest quintiles had greater odds of multimorbidity. Individuals with private health plans and who lived in urban areas had greater odds of multiple diseases. Individuals who lived in states with low and middle education levels had less multimorbidity compared to states with high education levels. With regard to income at state-level, the higher multimorbidity difference was demonstrated simply by comparing low with high income states (Table 2). The associations stratified by region revealed a similar pattern to the whole Brazil, except to Central Western region in relation to lack of association of overall multimorbidity and private health plan, geographical area (observed to Southeastern region too) and schooling (no dose-response relationship) (Table 3).

In the FA analysis, the KMO coefficient was 0.84. Two patterns of morbidities explained 92% of total variance, after rotation. The two components identified were: (1) cardiometabolic problems (High Blood Pressure, heart attack, angina, heart failure, stroke, hypercholesterolemia, diabetes and arthritis/rheumatism); (2) Respiratory/mental/muscle-skeletal disorders (arthritis/rheumatism, spinal column problem, asthma/wheezy bronchitis, COPD, work-related muscle-skeletal disorders, depression, bipolar disorder and kidney problem) (Supplementary table 2).

The adjusted multilevel analyses of the two factors are presented in Table 4. Overall, the results were similar to those observed in Table 2. Females, older people, those with less schooling, those with intermediate asset ownership quintiles and who had private health plans showed more burden of factors. People who lived in rural geographical areas showed less burden of the cardiometabolic factor. Individuals with partners presented less burden of the Respiratory/mental/muscle-skeletal factor compared to individuals who did not have a partner. Cardiometabolic and Respiratory/mental/muscle-skeletal factors were greater when state-level education and income were lower. The cardiometabolic factor presented similar associations as overall multimorbidity to stratified analysis. As for the Respiratory/mental/ muscle-skeletal factor did not show association with schooling in all regions (except to Northern) (Table 5).

Discussion

Multimorbidity frequency in Brazil is considerable; one in every five Brazilian adults had two or more morbidities and one in every ten had three or more morbidities. Individual and state-level inequalities suggest the complexity of factors and their relationship with multimorbidity occurrence. To our knowledge, this is the first representative Brazilian study to consider individual and contextual factors associated with multimorbidity and its clusters.

The study's national representativeness enables us to extrapolate frequencies for the whole Brazilian adult population. Considering 190,755,799 million adults in the most recent Brazilian population census (2010), we are able to infer that approximately 42.7 and 19.5 million Brazilian adults had two or more and three or more diseases, respectively. These results bring important challenges for the health system which will need to be more comprehensive in order to deal with the complexity of multimorbidity. Some of the issues are related to need to include multimorbidity in guidelines on reporting these problems to health professionals, as well as giving more emphasis to multimorbidity on health-related university curricula.

Relative comparisons with Western countries reveal similar occurrence of two or more diseases in Spain [23] (20.0%; CI95%: 18.8-21.2) and almost ten percentage points less than in Scotland [24] (31.1%, 25 or more years) and Canada[25] (30.9%; CI95% 29.5 – 32.4).In low and middle income countries (LMIC), estimates from countries (China, Ghana, India, Mexico, Russia, and South Africa) included in the WHO Study on global AGEing and adult health (SAGE) Wave-1 (2007/10), found 21.9% (CI95%: 20.9; 22.9) of multimorbidity occurrence (≥2 diseases from a list from eight morbidities)[5]. This occurrence varied from 20.3% in China to 34.7% in Russia. In the present analysis, we used more diseases to

construct multimorbidity (22 against eight in SAGE study). Even so, the prevalence found was, virtually, equal to these other LMIC countries, except for Russia.

In Brazil, our occurrence findings were slightly lower than the result found in a paper with same database (-2 pp). This is explained by the differences among diseases selected to measure multimorbidity and present an urgent call to more uniform multimorbidity operationalization. Comparing with located Brazilian results, the prevalences presented here were lower than frequencies found in a Southern Brazilian city (29.1%; CI95%: 27.1; 31.1 for ≥2 morbidities, and 14.3 %; CI95%: 12.8; 15.8 for ≥3 morbidities) despite the higher number of morbidities included in this study [10]. The difference observed may be attributed to socioeconomic characteristics of Brazilian states. The Southern states presented more income and schooling which tend to increase the occurrence of multimorbidity as observed in the results presented here.

In terms of socio-demographic characteristics, females and older adults presented more multimorbidity in all Brazilian regions as found in previous Brazilian [10 11] and international studies [26 27]. Women tend to use health services more and to live longer than males, these being factors which explain part of the higher frequency in this group. Survivors older adults tend to be exposed to more physiological damages in lifetime that contribute to chronic disease incidence [28]. In the same way, individuals who had partners had higher multimorbidity except to Central Western residents. The association between marital status should be more understanding through studies which include cultural assessment and its impact on chronic diseases development and diagnosis. One explanation is related to the fact that individuals with partner tend to use more health services increasing the probability of medical diagnosis [29].

Regarding socioeconomic variables, our results follow the pattern found in overall analysis of a worldwide study [27] and LMIC included in the SAGE study. Multimorbidity and its factors was not associated with wealth quintiles but presented association with education [5] regardless Brazilian regions. In the present analysis, the middle wealth quintile strata and their clusters present more multimorbidity whilst showing a negative dose-response relationship with education. These results may be explained by a strong relationship between educational attainment and all aspects of healthier life including those mainly related to better awareness of chronic disease risk factors [30 31]. Education level seems to be a more adequate socioeconomic indicator to evaluate multimorbidity inequalities due to its worldwide association with poor health outcomes and longevity, and the persistent effect overtime [30]. Except for the early effect of childhood health status on education [32 33], chronic diseases in adult life tend to increase the risk of poverty (wealth index) [34] but the effect on education tend to be less relevant since education is usually achieved is early life

Having private health plans was associated with multimorbidity and its factors, except to Central Western and Southern. This may be explained, by the relationship with self-reported diagnosis (a fundamental characteristic of the outcome). Individuals with health plans tend to use health services more frequently regardless the presence of chronic conditions[35 36] thus affording more diagnosis.

Individuals who lived in urban areas presented more multiple diseases. This was similar to results found in the adult population in South Africa [37] and Catalonia (Spain)[38]. In spite of little Brazilian evidence on the topic, as well as the social, cultural and environment differences between rural-urban residents, people from rural areas had more difficulty in accessing health services in Brazil [39] which may explain partially the differences between

rural and urban residents in our results of the occurrence of self-reported medical diagnosis of multiple diseases.

The state-level differences observed reveal a paradoxical association. Instead of individual inequalities are pro-rich, state-level differences are pro-poor. These results might be explained by demographic differences between states in Brazil which may not be fully adjusted with individual demographic variables included in the analysis. Low income and low education in Brazilian states are concentrated in North and Northeast regions and show the poorest health-related indicators[13]. The states further south (*Rio Grande do Sul* - 27.2% and *Santa Catarina* - 27.1%) present greater multimorbidity frequencies.

The two factors (cardiometabolic and respiratory/mental/muscle-skeletal) found have some similarity to recent evidence [40 41] mainly related to cardiometabolic patterns. The respiratory/mental/muscle-skeletal data found was similar to results found in a worldwide study of people aged 50 or over [42]. The majority of studies, especially with adult populations, found two or three patterns of diseases. These combinations of diseases suggest possible causal relationship between diseases or their risk factors [20]. The cardiometabolic pattern showed a more well know relationship between diseases. On the other hand, the relationship between respiratory, mental and muscle-skeletal disorders is less understood. The concomitant occurrence of these diseases is well described [43] but understanding the biological plausibility of causal relationships will be a challenge for new studies. As a first step, more detailed and specific information about onset of diseases will be needed. At the same time, the use of approaches related to network analysis can be useful for a better understanding of causal relationships [44]. Even so, the results presented here may contribute to the inclusion of recommendations in Brazilian clinical guidelines about the relationship

with chronic conditions, as well as to designing interventions/public policies considering the presence of multiple diseases in the same individual.

Some limitations of the study should be addressed. With the exception of depression, all the other morbidities were evaluated by self-reporting. This may provide a misclassification bias even though self-reported diagnosis is considered an adequate and common source of information used in population-based studies on multimorbidity [4 45 46]. Nevertheless, the lack of adequate information about diagnosis, including longitudinal information, limits the causal inference related to concomitant diseases expressed in factorial analysis. Furthermore, we are not able to evaluate the contextual determinants at neighborhood level which may produce more complete associations with state-level differences.

The absolute and relative number of Brazilian individuals with multimorbidity was high. Addressing the complexity of multiple disease management for at least 19 million people will be a challenge for the health system. The clusters of diseases identified might contribute to strategies for the prevention and clinical care of these diseases. State-level and individual inequalities increase the problem reinforcing the need of a wide lens to organize health services and to decrease the inequities among the Brazilian population.

Author contributions

BPN designed the article, obtained and analyzes the data, drafted the first version and revised the manuscript. ADPCF and FACF analyzed the data, and drafted and revised the manuscript. SP, DS, TRF, TNM, ET and LAF drafted and revised the manuscript. SBR designed the article, drafted and revised the manuscript. All authors approved the final version of the manuscript.

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Data sharing statement: All PNS data are available from the Brazilian Institute of Geography and Statistics website, located here: http://www.ibge.gov.br/home/estatistica/populacao/pns/2013/default_microdados.shtm.

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Tables and figures

Table 1. Description of the sample and multimorbidity frequency. Brazil, 2013.

Variables	n	%	Multimorbidity ≥2		Multimorbidity ≥3	
			%	95%CI	%	95%CI
Sex						
Male	25,920	44.9	17.5	16.6; 18.3	7.2	6.6; 7.8
Female	34,282	55.1	26.1	25.2; 27.0	12.6	12.0; 13.3
Age (in years)						
18 to 29	14,321	24.3	4.9	4.2; 5.6	1.2	0.9; 1.5
30 to 39	14,269	21.0	10.6	9.6; 11.5	2.8	2.3; 3.3
40 to 49	11,405	18.8	20.8	19.5; 22.1	7.8	7.0; 8.6
50 to 59	9,030	16.8	32.9	31.2; 34.6	15.5	14.3; 16.8
60 to 69	6,238	10.8	46.3	44.1; 48.6	24.7	22.8; 26.6
70 to 79	3,441	5.7	52.2	49.2; 55.2	30.9	28.0; 33.9
80 or more	1,498	2.6	52.8	48.6; 57.0	30.6	26.5; 34.7
Skin color*						
White	24,106	47.8	24.3	23.3; 25.4	11.6	10.8; 12.3
Black	5,631	9.2	22.2	20.2; 24.2	10.3	8.9; 11.6
Brown	29,512	41.7	19.8	18.9; 20.6	8.6	8.1; 9.2
Marital status						
Without partner	25,680	38.4	20.6	19.7; 21.5	9.9	9.3; 10.6
With partner	34,522	61.6	23.2	22.4; 24.1	10.4	9.7; 11.0
Schooling (in years)						
0	9,434	13.9	33.2	31.4; 35.0	16.3	14.9; 17.7
1-8	14,649	25.7	30.0	28.6; 31.4	16.1	14.9; 17.2
8-11	9,215	15.3	17.9	16.5; 19.3	7.5	6.5; 8.4
≥12	26,904	45.2	15.8	15.0; 16.7	5.9	5.4; 6.5
Wealth index (in quintiles)						
1º (High)	10,153	22.3	22.0	20.5; 23.6	9.3	8.3; 10.4
2º	11,531	22.4	22.3	21.0; 23.6	10.5	9.5; 11.5
3º	11,621	19.5	23.1	21.8; 24.4	10.6	9.7; 11.5
4º	14,380	21.0	22.2	20.9; 23.5	10.6	9.7; 11.6
5º (Low)	12,517	14.7	21.3	19.9; 22.7	9.9	8.9; 10.9
Private health plan						
No	43,834	69.4	21.1	20.3; 21.9	9.8	9.3; 10.4
Yes	16,368	30.6	24.8	23.5; 26.1	11.0	10.1; 12.0
Geographical area						
Urban	49,245	86.5	22.8	22.0; 23.5	10.5	10.0; 11.1
Rural	10,957	13.5	18.6	17.2; 20.0	8.0	7.1; 8.8
State-level education						

High	22,382	37.2	24.7	23.7; 25.7	11.7	10.9; 12.4
Middle	19,515	32.4	20.1	18.6; 21.7	9.3	8.3; 10.4
Low	18,305	30.4	19.0	18.0; 20.1	8.0	7.3; 8.6
State-level income						
High	21,683	36.0	24.6	23.6; 25.7	11.6	10.8; 12.3
Middle	18,087	30.0	21.8	20.2; 23.3	10.5	9.5; 11.6
Low	20,432	33.9	18.2	17.2; 19.2	7.5	6.9; 8.1
Total	60,202	100.0	22.2	21.5; 22.9	10.2	9.7; 10.7

Table 2. Adjusted multilevel models of multimorbidity with independent variables. Brazil, 2013.

Variables	Multimorbidity (≥2)						Multimorbidity (≥3)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%
Sex (ref: male)												
Female	**1.84**	**1.76; 1.94**	**1.85**	**1.77; 1.94**	**1.85**	**1.77; 1.94**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.09**
Age (in years)	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**
Skin color* (ref: White)												
Black	1.07	0.99; 1.16	1.08	0.99; 1.17	1.08	0.99; 1.17	1.09	0.98; 1.21	1.09	0.98; 1.21	1.09	0.98; 1.21
Brown	1.01	0.96; 1.06	1.01	0.96; 1.07	1.01	0.96; 1.07	0.97	0.91; 1.04	0.97	0.91; 1.04	0.97	0.91; 1.04
Marital status (ref: Without partner)												
With partner	**1.13**	**1.08; 1.18**	**1.13**	**1.08; 1.19**	**1.13**	**1.08; 1.19**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**
Schooling (in years) [#] (ref: ≥12)												
8-11	**1.19**	**1.11; 1.28**	**1.19**	**1.10; 1.28**	**1.19**	**1.10; 1.28**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**
1-8	**1.41**	**1.33; 1.51**	**1.41**	**1.33; 1.50**	**1.41**	**1.33; 1.50**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**
0	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.41**	**1.27; 1.56**	**1.41**	**1.28; 1.56**	**1.41**	**1.28; 1.56**
Wealth index (in quintiles) (ref: High)												
2º	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**
3º	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**
4º	1.05	0.96; 1.14	1.05	0.97; 1.14	1.05	0.97; 1.14	1.09	0.98; 1.22	1.10	0.98; 1.23	1.10	0.98; 1.23
5º (Low)	0.91	0.83; 1.00	0.92	0.84; 1.01	0.92	0.84; 1.01	0.95	0.84; 1.08	0.95	0.84; 1.08	0.95	0.84; 1.08
Private health plan (ref: no)												
Yes	**1.15**	**1.08; 1.21**	**1.15**	**1.08; 1.20**	**1.15**	**1.08; 1.20**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**
Geographical area (ref: urban)												
Rural	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**
State-level education (ref: High)												
Middle			**0.82**	**0.71; 0.94**					**0.76**	**0.64; 0.90**		
Low			**0.83**	**0.72; 0.96**					**0.76**	**0.64; 0.90**		
State-level income (ref: High)												
Middle					0.89	0.77; 1.04					0.88	0.73; 1.05
Low					**0.82**	**0.71; 0.95**					**0.75**	**0.63; 0.89**

Table 3. Adjusted multilevel models of multimorbidity with independent variables stratified by region. Brazil, 2013.

Variables	Northern region		Northeastern region		Central Western region		Southeastern region		Southern region	
	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%
Sex (ref: male)										
Female	**1.81**	**2.06**	**1.96**	**2.08**	**2.22**	**2.37**	**1.62**	**1.61**	**1.84**	**2.04**
	1.62; 2.02	**1.75; 2.43**	**1.8; 2.14**	**1.84; 2.36**	**1.94; 2.54**	**1.97; 2.86**	**1.48; 1.78**	**1.43; 1.82**	**1.63; 2.08**	**1.73; 2.39**
Age (in years)	**1.05**	**1.06**	**1.06**	**1.06**	**1.07**	**1.07**	**1.05**	**1.05**	**1.06**	**1.06**
	1.05; 1.06	**1.05; 1.06**	**1.06; 1.06**	**1.06; 1.06**	**1.06; 1.07**	**1.06; 1.07**	**1.05; 1.06**	**1.05; 1.06**	**1.05; 1.06**	**1.06; 1.07**
Marital status (ref: Without partner)										
With partner	**1.13**	**1.17**	**1.16**	**1.23**	1.00	0.93	**1.15**	**1.22**	**1.16**	**1.19**
	1.02; 1.27	**1; 1.38**	**1.07; 1.27**	**1.09; 1.39**	0.87; 1.14	0.78; 1.11	**1.05; 1.26**	**1.08; 1.38**	**1.02; 1.32**	**1.01; 1.4**
Skin color* (ref: White)										
Black	1.01	1.06	1.12	1.14	0.94	0.89	1.11	1.15	1.00	0.98
	0.82; 1.23	0.79; 1.42	0.97; 1.3	0.94; 1.39	0.74; 1.21	0.63; 1.26	0.96; 1.29	0.95; 1.4	0.76; 1.31	0.7; 1.38
Brown	0.92	0.92	0.96	0.93	1.13	1.14	1.07	1.02	1.08	0.88
	0.81; 1.04	0.76; 1.1	0.87; 1.05	0.81; 1.05	0.98; 1.29	0.95; 1.36	0.97; 1.18	0.89; 1.16	0.91; 1.27	0.71; 1.09
Schooling (in years) [#] (ref: more educated)										
III	1.17	1.12	1.10	0.95	1.16	1.32	**1.35**	**1.47**	1.12	1.27
	0.99; 1.39	0.86; 1.47	0.95; 1.28	0.76; 1.18	0.94; 1.42	0.99; 1.75	**1.18; 1.55**	**1.22; 1.78**	0.94; 1.35	0.99; 1.62
II	**1.23**	**1.36**	**1.33**	**1.35**	**1.33**	**1.32**	**1.65**	**1.89**	**1.43**	**1.73**
	1.05; 1.44	**1.08; 1.71**	**1.18; 1.51**	**1.14; 1.6**	**1.11; 1.59**	**1.03; 1.68**	**1.46; 1.86**	**1.61; 2.22**	**1.22; 1.68**	**1.41; 2.13**
I (less educated)	**1.32**	**1.48**	**1.38**	**1.36**	1.17	1.25	**1.43**	**1.40**	1.19	**1.46**
	1.12; 1.55	**1.16; 1.88**	**1.21; 1.58**	**1.13; 1.65**	0.94; 1.46	0.94; 1.68	**1.22; 1.67**	**1.14; 1.71**	0.97; 1.47	**1.12; 1.89**
Wealth index (in quintiles) (ref: High)										
2º	1.03	0.92	1.07	1.21	**1.29**	1.17	1.03	1.09	**1.22**	1.25
	0.83; 1.29	0.67; 1.27	0.91; 1.26	0.96; 1.52	**1.05; 1.58**	0.89; 1.55	0.90; 1.18	0.91; 1.3	**1.04; 1.44**	1.00; 1.57
3º	1.21	0.98	**1.26**	**1.40**	1.19	1.10	1.02	1.05	**1.42**	**1.33**
	0.98; 1.51	0.71; 1.34	**1.07; 1.48**	**1.11; 1.76**	0.95; 1.48	0.82; 1.48	0.89; 1.18	0.87; 1.27	**1.18; 1.7**	**1.05; 1.69**
4º	0.90	0.82	1.07	1.22	1.13	1.18	0.96	0.98	**1.34**	1.30
	0.72; 1.12	0.60; 1.11	0.91; 1.26	0.97; 1.53	0.9; 1.42	0.88; 1.59	0.82; 1.12	0.79; 1.20	**1.09; 1.66**	1.00; 1.7
5º (Low)	0.80	0.74	0.93	0.97	1.05	1.16	0.94	1.13	0.92	0.85
	0.64; 1.01	0.53; 1.03	0.78; 1.12	0.76; 1.25	0.80; 1.36	0.83; 1.62	0.77; 1.14	0.88; 1.45	0.71; 1.20	0.61; 1.19

Private health plan (ref: no)										
Yes	1.15	**1.29**	**1.23**	**1.22**	1.15	1.16	**1.12**	1.05	1.10	0.91
	0.98; 1.35	**1.02; 1.61**	**1.09; 1.39**	**1.04; 1.44**	0.99; 1.34	0.95; 1.41	**1.01; 1.24**	0.92; 1.2	0.96; 1.25	0.77; 1.09
Geographical área (ref: urban)										
Rural	0.89	**0.76**	**0.84**	**0.75**	0.91	0.85	0.88	0.82	**0.82**	0.83
	0.77; 1.03	**0.61; 0.94**	**0.75; 0.94**	**0.64; 0.88**	0.75; 1.11	0.65; 1.11	0.76; 1.02	0.67; 1.00	**0.68; 0.97**	0.67; 1.04

Note: MM = Multimorbidity

Table 4. Adjusted multilevel models of patterns of diseases (factors) with independent variables. Brazil, 2013.

Variables	Factor 1 (Cardiometabolic)						Factor 2 (Respiratory/mental/ muscle-skeletal)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%
Sex (ref: male)												
Female	**.024**	**.022; .026**	**.024**	**.022; .026**	**.024**	**.022; .026**	**.038**	**.036; .040**	**.038**	**.036; .040**	**.038**	**.036; .040**
Age (in years)	**.004**	**.004; .004**	**.004**	**.004; .004**	**.004**	**.004; .004**	**.001**	**.001; .001**	**.001**	**.001; .001**	**.001**	**.001; .001**
Skin color* (ref: White)												
Black	**.007**	**.003; .010**	**.007**	**.003; .010**	**.007**	**.003; .010**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**
Brown	.001	-.001; .004	.002	-.001; .004	.002	-.001; .004	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**
Marital status (ref: Without partner)												
With partner	.000	-.002; .002	.000	-.002; .002	.000	-.002; .002	**-.005**	**-.007; -.002**	**-.005**	**-.007; -.003**	**-.005**	**-.007; -.003**
Schooling (in years) [#] (ref: ≥12)												
8-11	**.013**	**.010; .016**	**.013**	**.010; .016**	**.013**	**.010; .016**	**.004**	**.001; .008**	**.005**	**.002; .008**	**.005**	**.002; .008**
1-8	**.021**	**.018; .023**	**.021**	**.018; .023**	**.021**	**.018; .023**	**.011**	**.008; .014**	**.011**	**.008; .014**	**.011**	**.008; .014**
0	**.014**	**.010; .017**	**.014**	**.010; .017**	**.014**	**.010; .017**	.001	-.003; .004	.001	-.003; .005	.001	-.003; .005
Wealth index (in quintiles) (ref: High)												
2º	**.007**	**.004; .010**	**.007**	**.004; .010**	**.007**	**.004; .010**	**.005**	**.001; .008**	**.005**	**.001; .008**	**.005**	**.001; .008**
3º	**.009**	**.006; .013**	**.009**	**.006; .013**	**.009**	**.006; .013**	**.010**	**.006; .014**	**.010**	**.006; .014**	**.010**	**.006; .014**
4º	**.006**	**.002; .009**	**.006**	**.002; .009**	**.006**	**.002; .009**	.004	.000; .008	.004	.000; .008	.004	.000; .008
5º (Low)	-.003	-.007; .001	-.003	-.007; .001	-.003	-.007; .001	.001	-.004; .005	.001	-.004; .005	.001	-.004; .005
Private health plan (ref: no)												
Yes	**.006**	**.004; .009**	**.006**	**.004; .009**	**.006**	**.004; .009**	**.007**	**.005; .010**	**.007**	**.005; .010**	**.007**	**.005; .010**
Geographical area (ref: urban)												
Rural	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	-.002	-.005; .002	-.002	-.005; .002	-.002	-.005; .002
State-level education (ref: High)												
Middle			**-.010**	**-.016; -.004**					**-.016**	**-.027; -.005**		
Low			**-.008**	**-.015; -.002**					**-.018**	**-.029; -.006**		
State-level income (ref: High)												
Middle					-.006	-.012; .001					-.011	-.022; .001
Low					**-.009**	**-.016; -.003**					**-.017**	**-.028; -.006**

Table 5. Adjusted multilevel models of multimorbidity factors with independent variables stratified by region. Brazil, 2013.

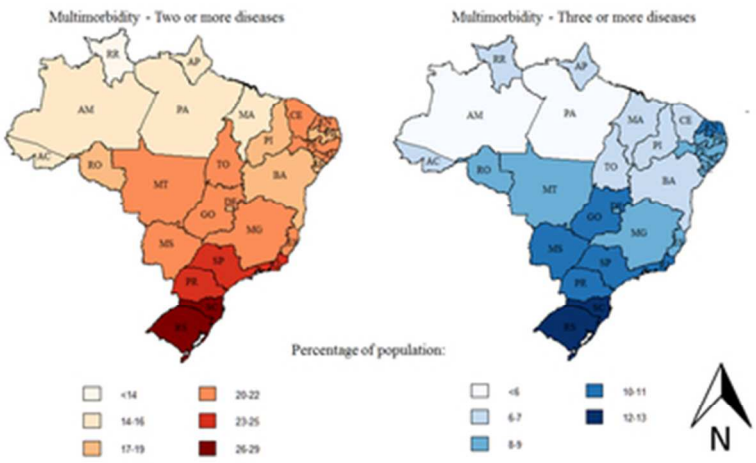
Variables	Northern region		Northeastern region		Central Western region		Southeastern region		Southern region	
	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%
Sex (ref: male)										
Female	**0.022**	**0.023**	**0.027**	**0.030**	**0.029**	**0.050**	**0.020**	**0.041**	**0.023**	**0.061**
	0.018; 0.026	**0.019; 0.027**	**0.023; 0.03**	**0.027; 0.034**	**0.023; 0.034**	**0.044; 0.056**	**0.015; 0.024**	**0.036; 0.045**	**0.017; 0.03**	**0.053; 0.069**
Age (in years)	**0.003**	**0.001**	**0.004**	**0.001**	**0.004**	**0.001**	**0.004**	**0.001**	**0.004**	**0.002**
	0.003; 0.003	**0.001; 0.001**	**0.003; 0.004**	**0.001; 0.001**	**0.004; 0.004**	**0.001; 0.002**	**0.004; 0.004**	**0.001; 0.001**	**0.004; 0.004**	**0.001; 0.002**
Marital status (ref: Without partner)										
With partner	0.001	-0.002	0.000	-0.002	**-0.007**	**-0.013**	0.001	-0.005	0.002	**-0.010**
	-0.003; 0.005	-0.006; 0.003	-0.003; 0.004	-0.005; 0.002	**-0.013; -0.002**	**-0.02; -0.007**	-0.003; 0.005	-0.010; 0.000	-0.004; 0.009	**-0.018; -0.002**
Skin color* (ref: White)										
Black	0.005	-0.007	**0.007**	-0.003	-0.001	**-0.021**	**0.008**	**-0.011**	0.013	-0.018
	-0.002; 0.013	-0.015; 0.001	**0.001; 0.013**	-0.01; 0.003	-0.011; 0.009	**-0.033; -0.01**	**0.001; 0.016**	**-0.02; -0.003**	-0.001; 0.026	-0.036; 0.000
Brown	-0.002	**-0.007**	-0.001	-0.003	0.004	-0.003	0.004	-0.002	0.005	0.004
	-0.007; 0.002	**-0.012; -0.002**	-0.005; 0.003	-0.008; 0.001	-0.001; 0.01	-0.010; 0.004	-0.001; 0.009	-0.008; 0.003	-0.003; 0.014	-0.007; 0.015
Schooling (in years) [#] (ref: more educated)										
III	0.006	**0.007**	**0.011**	0.000	**0.012**	-0.001	**0.016**	0.007	**0.019**	0.010
	0.000; 0.011	**0.001; 0.013**	**0.006; 0.017**	-0.006; 0.006	**0.004; 0.02**	-0.011; 0.008	**0.010; 0.023**	0.000; 0.014	**0.01; 0.028**	-0.002; 0.021
II	**0.009**	0.005	**0.015**	**0.006**	**0.016**	-0.001	**0.029**	**0.019**	**0.037**	**0.020**
	0.003; 0.014	-0.001; 0.011	**0.010; 0.020**	**0.001; 0.012**	**0.009; 0.024**	-0.01; 0.008	**0.023; 0.035**	**0.013; 0.026**	**0.028; 0.046**	**0.009; 0.031**
I (less educated)	**0.014**	**0.008**	**0.010**	0.002	**0.015**	-0.009	**0.022**	-0.002	**0.016**	-0.005
	0.008; 0.02	**0.001; 0.014**	**0.004; 0.015**	-0.004; 0.008	**0.005; 0.025**	-0.021; 0.002	**0.014; 0.03**	-0.011; 0.007	**0.004; 0.027**	-0.02; 0.01
Wealth index (in quintiles) (ref: High)										
2º	0.005	0.005	0.005	0.002	0.008	0.004	0.004	-0.003	**0.011**	**0.017**
	-0.003; 0.013	-0.004; 0.013	-0.002; 0.011	-0.005; 0.009	-0.001; 0.016	-0.005; 0.014	-0.002; 0.011	-0.01; 0.004	**0.003; 0.002**	**0.007; 0.028**
3º	**0.009**	0.004	**0.012**	**0.010**	0.002	0.002	0.004	0.002	**0.012**	**0.027**
	0.001; 0.017	-0.004; 0.013	**0.005; 0.018**	**0.003; 0.017**	-0.007; 0.011	-0.008; 0.013	-0.003; 0.011	-0.005; 0.01	**0.003; 0.021**	**0.015; 0.039**

4º	0.004	-0.001	0.005	0.004	0.005	0.005	0.003	-0.007	0.009	**0.019**
	-0.004; 0.011	-0.01; 0.007	-0.002; 0.011	-0.003; 0.011	-0.005; 0.014	-0.006; 0.016	-0.004; 0.011	-0.015; 0.001	-0.002; 0.02	**0.005; 0.033**
5º (Low)	-0.004	-0.009	-0.001	0.004	0.001	0.004	-0.006	-0.004	-0.012	0.012
	-0.012; 0.004	-0.017; 0.000	-0.009; 0.006	-0.003; 0.012	-0.010; 0.012	-0.008; 0.017	-0.015; 0.004	-0.015; 0.006	-0.026; 0.002	-0.006; 0.029
Private health plan (ref: no)										
Yes	**0.009**	**0.009**	**0.010**	**0.008**	0.007	**0.009**	0.002	**0.008**	0.005	0.001
	0.003; 0.015	**0.003; 0.016**	**0.006; 0.015**	**0.003; 0.013**	0.000; 0.013	**0.001; 0.016**	-0.003; 0.006	**0.002; 0.013**	-0.002; 0.012	-0.008; 0.01
Geographical área (ref: urban)										
Rural	**-0.007**	0.004	**-0.008**	**-0.006**	**-0.009**	**-0.001**	-0.007	**-0.010**	-0.008	0.009
	-0.012; -0.002	-0.002; 0.009	**-0.013;-0.004**	**-0.011;-0.001**	**-0.018; -0.001**	**-0.01; 0.009**	-0.014; 0.000	**-0.018;-0.001**	-0.017; 0.002	-0.003; 0.021

Note: Factor 1: cardiometabolic; factor 2: (Respiratory/mental/ muscle-skeletal)

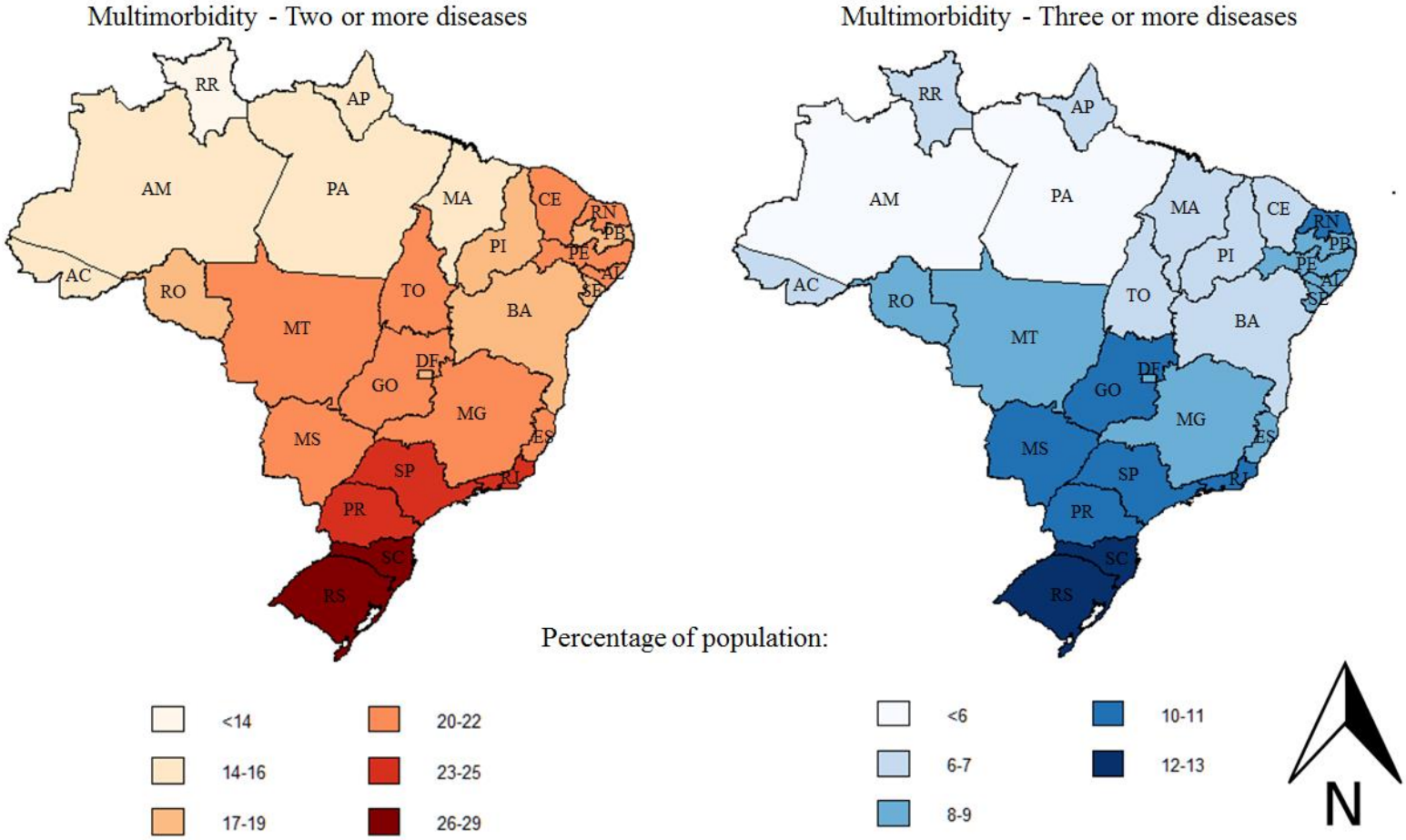
Supplementary table 1. Individual prevalence, duration and number of comorbidities for each morbidity evaluated. Brazil, 2013.

Morbidities	Individual prevalence		Duration of disease	Number of comorbidities
	%	(95%CI)	Mean (median; Q25-Q75)	Mean (median; Q25-Q75)
High Blood Pressure	22.3	21.7 - 23.0	13.1 (9; 3-18)	2.3 (2; 1-3)
Spinal column problem	19.0	18.3 - 19.7	14.7 (10; 4-21)	2.3 (2; 1-3)
Hypercholesterolemia	8.4	8.0 - 8.8	6.9 (3; 1-9)	2.3 (2; 1-3)
Arthritis/rheumatism	6.7	6.4 - 7.1	14.6 (10; 3-20)	3.0 (3; 2-4)
Diabetes	6.5	6.2 - 6.9	11.3 (6; 2-15)	2.9 (3; 2-4)
Asthma/wheezy bronchitis	4.4	4.1 - 4.8	25.1 (23; 13-35)	2.4 (2; 1-3)
Depression	4.2	3.9 - 4.5	-	2.9 (3; 2-4)
Work-related muscle-skeletal disorders	2.5	2.2 - 2.8	7.5 (5; 2-11)	2.5 (2; 1-3)
Cancer	1.9	1.7 - 2.2	8.5 (6; 2-13)	2.8 (2; 2-4)
Another heart disease	1.9	1.6 - 2.1	13.9 (9; 3-20)	3.1 (3; 2-4)
Stroke	1.6	1.4 - 1.8	10.2 (6; 2-13)	3.4 (3; 2-5)
Kidney problem	1.5	1.3 - 1.7	13.5 (9; 3-20)	3.2 (3; 2-4)
Heart attack	1.3	1.2 - 1.5	12.4 (7; 2-18)	4.0 (4; 3-5)
Heart failure	1.2	1.1 - 1.4	13.2 (8; 4-19)	4.0 (4; 2-5)
Bronchitis	1.0	0.8 - 1.1	23.2 (20; 9-32)	3.3 (3; 2-5)
Angina	0.8	0.7 - 0.9	15.5 (11; 5-21)	4.5 (4; 3-6)
Emphysema	0.5	0.4 - 0.6	14.9 (9; 3-18)	3.7 (3; 2-5)
Another lung disease	0.5	0.4 - 0.6	16.2 (12; 5-24)	2.8 (2; 1-4)
Bipolar disorder	0.4	0.3 - 0.5	11.3 (8; 4-16)	3.1 (3; 2-4)
Another mental disease	0.3	0.2 - 0.4	2.8 (2; 1-4)	2.5 (2; 1-3)
Schizophrenia	0.2	0.2 - 0.3	19.7 (19; 8-26)	2.7 (3; 2-3)
Obsessive Compulsive Disorder (OCD)	0.2	0.1 - 0.2	14.5 (12; 6-21)	3.4 (3; 2-4)



Multimorbidity frequency by Brazilian states. Brazil, 2013

39x21mm (300 x 300 DPI)


Multimorbidity - Two or more diseases
Multimorbidity - Three or more diseases
RR
AP
AM
PA
MA
CE
RN
PB
PI
PE
AL
SE
AC
RO
TO
BA
MT
DF
GO
MG
ES
MS
SP
RJ
PR
SC
RS
Percentage of population:
<14
14-16
17-19
20-22
23-25
26-29
<6
6-7
8-9
10-11
12-13
N

Supplementary table 2. Factor analysis. Brazil, 2013.

Morbidities	Factor 1	Factor 2
High Blood Pressure	0.77	
Heart attack	0.79	
Angina	0.68	
Heart failure	0.69	
Stroke	0.58	
Hypercholesterolemia	0.57	
Diabetes	0.62	
Arthritis/rheumatism	0.30	0.37
Spinal column problem		0.45
Asthma/wheezy bronchitis		0.57
COPD		0.63
Work-related muscle-skeletal disorders		0.45
Depression		0.46
Bipolar disorder		0.46
Kidney problem		0.31
Cancer	-	-
Eigenvalor	4.46	1.11
Explained variance %*	0.73 (0.69)	0.18 (0.47)
KMO	0.84	

*Before oblique rotation (after oblique rotation)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Contextual and individual inequalities of multimorbidity in Brazilian adults: a cross-sectional national-based study

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Comorbidity, Multimorbidity, Chronic disease, Statistical disease clustering, Multilevel Analysis

Title page

Title: Contextual and individual inequalities of multimorbidity in Brazilian adults: a cross-sectional national-based study

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Key-words: Comorbidity; Multimorbidity; Chronic disease; Statistical disease clustering; Multilevel Analysis.

Word count: 3137

Abstract

Objectives: The study aims to evaluate the magnitude of multimorbidity in Brazilian adults, as well to measure their association with individual and contextual factors stratified by Brazilian states and regions.

Methods: A national-based cross-sectional study was carried out in 2013 with Brazilian adults. Multimorbidity was evaluated by a list of 22 physical and mental morbidities (based on self-reported medical diagnosis and Patient Health Questionnaire 9 for depression). The outcome was analyzed taking ≥2 and ≥3 diseases as cut-off points. Factor analysis (FA) was used to identify disease patterns and multilevel models were used to test association with individual and contextual variables.

Results: The sample was comprised of 60,202 individuals. Multimorbidity frequency was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. In the multilevel adjusted models, females, older people, those living with a partner and having less schooling presented more multiple diseases. No linear association was found according to wealth index but greater outcome frequency was found in individuals with mid-range wealth index. Living in states with higher levels of education and wealthier states was associated with greater multimorbidity. Two patterns of morbidities (cardiometabolic problems and Respiratory/mental/muscle-skeletal disorders) explained 92% of total variance. The relationship of disease patterns with individual and contextual variables was similar to the overall multimorbidity, with differences among Brazilian regions.

Conclusions: In Brazil, at least 19 million adults had multimorbidity. Frequency is similar to that found in other LMIC. Contextual and individual social inequalities were observed.

Strengths and limitations of this study

- Comprehensive information about multimorbidity is still scarce in Brazil
- As far as we are aware, this is among the first information about multimorbidity assessment of individual and contextual factors in a sample representative of the whole of Brazil
- Multimorbidity is a challenge to the Brazilian health system due to its high frequency (two in every ten adults had ≥2 diseases and one in every ten had ≥3 diseases, representing at least 19 million Brazilians) and the interplay of individual and contextual characteristics associated with the problem. Differences within the country were observed.
- Except for depression, other morbidities were evaluated by self-reporting and we are not able to evaluate the contextual determinants at neighborhood level

Introduction

Multimorbidity is a current and worldwide public health problem mainly due to its high frequency (>60% in adults) and its association with negative outcomes [1-4]. Most evidence is from High Income Countries [4] but results from Low and Middle Income Countries (LMIC) are also available and increasing in the literature [5-8], including epidemiological information about multimorbidity in Brazilian cities [9-11].

Similar to international evidence, multimorbidity in Brazil is greater in females and increases according to age. Socioeconomic inequalities are also observed mainly related to educational differences whereas multiple disease is more frequent in adults and elderly with less schooling and lower socioeconomic status [10 11].

However, as far as we are aware, Brazilian evidence on multimorbidity for the entire country is scarce. Only recently, a paper evaluating epidemiology of multimorbidity in Brazil was published [12]. The authors found a 24.2% (95% CI 23.5–24.9) prevalence rate of multimorbidity [12] and correlates were similar to Brazilian located previous studies ([10 11].

Brazil is the 5th most populous country in the world with more than 200 million people. Furthermore, it is marked by historic social inequalities in different health aspects comprising the occurrence of chronic diseases including both physical and mental disorders [13-15]. Understanding the occurrence and patterns of multimorbidity in the whole country can be relevant for Brazilian Unified Health System management of the challenges resulting from the rapid demographic and epidemiological transitions that have occurred in recent years. Additionally, identifying and comprehending the contextual and individual differences

surrounding multimorbidity occurrence helps policy-makers to prioritize and promote health actions and interventions related to multimorbidity management.

Thus, the aim of this study was to evaluate the frequency and patterns of multimorbidity in Brazilian adults, as well to measure their association with individual and contextual factors stratified by Brazilian states and regions.

Methods

This was a cross-sectional study using population-based data from the Brazilian National Health Survey (*Pesquisa Nacional de Saúde - PNS)* carried out in Brazil in 2013. The survey was conducted by *Instituto Brasileiro de Geografia e Estatística (IBGE)* and the Ministry of Health. The sample is representative of people living in permanent housing, located in urban or rural areas, covering the country's five major geographical regions, its 26 states and Federal District.

Sampling was done in three stages, the first being the selection of census tracts, followed by households and, finally, individuals aged 18 or over. More details about the sampling process can be found elsewhere[16 17].

Multimorbidity was evaluated by using a list of all 22 self-reported morbidities available in the study, 21 of which were based on self-reported medical diagnosis, while depression was based on the Patient Health Questionnaire-9(PHQ-9)[18]. The question applied to measure each disease based on self-reported medical diagnosis was: *"Has any physician already diagnosed you as having [each disease]?"*.The following morbidities were included: High Blood Pressure - HBP; Spinal column problem; Hypercholesterolemia; Depression; Diabetes; Arthritis/rheumatism; Asthma/wheezy bronchitis; Work-related muscle-skeletal disorders; Cancer; Other heart disease; Stroke; Kidney problem; Heart attack; Heart failure; Bronchitis; Angina; Emphysema; Other lung disease; Bipolar disorder; Other mental disease; Schizophrenia; and Obsessive Compulsive Disorder (OCD). Multimorbidity was evaluated by two cut-off points as per the literature[4 19]: ≥2and ≥3morbidities. Women who had HBP or diabetes only during pregnancy were considered as not having these diseases.

Independent variables were sex (male; female), age (continuous), skin color (white; black; and brown - Asian-Brazilian and indigenous were not shown because they represented less than 1.6% of the sample), marital status (without partner; with partner), schooling in years (0: No schooling; 1-8: incomplete primary school; 8-11: complete primary school and incomplete secondary school; ≥12: complete secondary school up to complete higher education), wealth index in quintiles (based on ownership of bathroom, car, motorcycle, refrigerator, washing machine, DVD player, TV, landline telephone, microcomputer and microwave oven), private health plan (no; yes), geographical area (urban; rural); state-level education in terciles – proportion of literacy rate obtained from IBGE, 2010 and state-level income in terciles (nominal income per capita - average monthly value - in permanent private housing obtained from IBGE, 2010).

Statistical analyses were performed using Stata 12.1 software and the *svy* command was used, which takes into consideration sample weights. Sample weights were defined for the primary sampling units, households and all inhabitants, as well as for the selected inhabitant. Complete information about PNS sample weights and sampling process have been published elsewhere [16 17]. The results from the sample were expanded for the Brazilian population.

Descriptive analysis was based on the calculation of prevalence and its respective confidence intervals. Factor analysis (FA) was performed to identify patterns of morbidities[20]. This analysis was based on tetrachoric correlation, this being more appropriate than Pearson's correlation for dichotomous variables [21]. Before FA analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett sphericity tests were used to evaluate the applicability of this approach. After the first evaluation of the model, some variables were encompassed (bronchitis, emphysema and other lung disease to other respiratory problems - COPD) and others excluded (schizophrenia, Obsessive Compulsive Disorder, another mental disease and another heart disease) in order to

obtain a better model fit regarding KMO and Bartlett sphericity tests. Oblique (oblimin or promax) rotation was performed. In order to establish the number of components to be retained, we used Cattel graphics, Kaiser criteria (eigenvalue>1) and minimum explained variance (>10% for each component). Variables with loadings |≥0.3| were kept [22]. Through factorial analysis, we obtained the predicted scores of morbidities (factors).

Multilevel models were performed to account for state-level variance, with the individuals as the first level and the state of residence as the second level. First, the models were initially adjusted without inclusion of the independent variables (null model) to test the initial variance attributable to the state accounting for approximately 1% ($p<0.05$) of variance for the four analyses (Multimorbidity ≥2; Multimorbidity ≥3, factor 1 and factor 2). Then, we performed a logistic regression model for multimorbidity (≥2 and ≥3 morbidities) and linear regression models to evaluate the association of factors (patterns) of diseases and independent variables. We included sex, age, skin color, marital status, schooling in years, private health plan, geographical area, state-level education and income in these models. Stratified region-level analyzes were performed to better understanding disparities among states.

The study was approved by the National Research Ethics Commission on July 8, 2013, under No. 10853812.7.0000.0008. All respondents signed a free and informed consent statement form prior to data collection

Results

The sample was comprised of 60,202 adults. The most frequent diseases were High Blood Pressure (22.3%) and Spinal column problem (19.0%). Angina, emphysema, other lung disease, bipolar disorder, other mental disease, schizophrenia and Obsessive Compulsive Disorder (OCD) were present in less than 1% of the sample. Lung disease problems showed, on average, longer duration of disease. Greater comorbidities were observed for individuals with health problems (heart attack; heart failure and angina). The mean range of comorbidities was from 2.3 to 4.5 diseases (Supplementary table 1).

Females comprised 55.1% of the sample and mean age was 43.7 years (SD=17.0), ranging from 18 to 101. Most individuals reported white skin color (47.8%) followed by brown (41.7%). Almost two thirds lived with a partner. Out of the total sample, 45.2% had ≥12 years of schooling and 13.9% had zero schooling. Less than one third had a private health plan and 13.5% lived in rural areas (Table 1). The mean average proportion of literacy rate at the state-level was 7.3%, ranging from 3.3% to 22.5%. The average monthly value of nominal income per capita was R$ 1,069 (approximately US$ 644 in 2010).

The occurrence of multimorbidity was 22.2% (CI95% 21.5; 22.9) for ≥2 morbidities and 10.2% (CI95% 9.7; 10.7) for ≥3 morbidities. Irrespective of cut-off point, multimorbidity was higher in females, older people, individuals reporting white skin color, who lived with a partner, had less schooling, had a private health plan and living in urban areas. At state-level, multimorbidity was more frequent in states with higher education levels and wealthier states (Table 1). States in the South of Brazil showed the highest occurrence of multimorbidity (Supplementary figure 1),

In the adjusted multilevel models, females had 1.86 (CI95% 1.78; 1.95) and 1.97(CI95% 1.85; 2.10) more odds of multimorbidity than males, for ≥2 and ≥3 morbidities, respectively. In all cases, every additional year of age increased by 1.06 times the odds of multiples diseases. Self-reported skin color was not associated with multimorbidity in the adjusted models. On average, living with a partner increased by 1.15 times the odds of the outcome. Compared to individuals with ≥12 years of schooling, adults with 1-8 years of schooling had more odds of multimorbidity (OR 1.40 - CI95% 1.32; 1.49, for ≥2 diseases and OR 1.58 CI95% 1.45; 1.72, for ≥3 morbidities). In general, adults in the second and third wealthiest quintiles had greater odds of multimorbidity. Individuals with private health plans and who lived in urban areas had greater odds of multiple diseases. Individuals who lived in states with low and middle education levels had less multimorbidity compared to states with high education levels. With regard to income at state-level, the higher multimorbidity difference was demonstrated simply by comparing low with high income states (Table 2). The associations stratified by region revealed a similar pattern to the whole Brazil, except to Central Western region in relation to lack of association of overall multimorbidity and private health plan, geographical area (observed to Southeastern region too) and schooling (no dose-response relationship) (Table 3).

In the FA analysis, the KMO coefficient was 0.84. Two patterns of morbidities explained 92% of total variance, after rotation. The two components identified were: (1) cardiometabolic problems (High Blood Pressure, heart attack, angina, heart failure, stroke, hypercholesterolemia, diabetes and arthritis/rheumatism); (2) Respiratory/mental/muscle-skeletal disorders (arthritis/rheumatism, spinal column problem, asthma/wheezy bronchitis, COPD, work-related muscle-skeletal disorders, depression, bipolar disorder and kidney problem) (Supplementary table 2).

The adjusted multilevel analyses of the two factors are presented in Table 4. Overall, the results were similar to those observed in Table 2. Females, older people, those with less schooling, those with intermediate asset ownership quintiles and who had private health plans showed more burden of factors. People who lived in rural geographical areas showed less burden of the cardiometabolic factor. Individuals with partners presented less burden of the Respiratory/mental/muscle-skeletal factor compared to individuals who did not have a partner. Cardiometabolic and Respiratory/mental/muscle-skeletal factors were greater when state-level education and income were lower. The cardiometabolic factor presented similar associations as overall multimorbidity to stratified analysis. As for the Respiratory/mental/ muscle-skeletal factor did not show association with schooling in all regions (except to Northern) (Table 5).

Discussion

Multimorbidity frequency in Brazil is considerable; one in every five Brazilian adults had two or more morbidities and one in every ten had three or more morbidities. Individual and state-level inequalities suggest the complexity of factors and their relationship with multimorbidity occurrence. To our knowledge, this is the first representative Brazilian study to consider individual and contextual factors associated with multimorbidity and its clusters.

The study's national representativeness enables us to extrapolate frequencies for the whole Brazilian adult population. Considering 190,755,799 million adults in the most recent Brazilian population census (2010), we are able to infer that approximately 42.7 and 19.5 million Brazilian adults had two or more and three or more diseases, respectively. These results bring important challenges for the health system which will need to be more comprehensive in order to deal with the complexity of multimorbidity. Some of the issues are related to need to include multimorbidity in guidelines on reporting these problems to health professionals, as well as giving more emphasis to multimorbidity on health-related university curricula.

Relative comparisons with Western countries reveal similar occurrence of two or more diseases in Spain [23] (20.0%; CI95%: 18.8-21.2) and almost ten percentage points less than in Scotland [24] (31.1%, 25 or more years) and Canada[25] (30.9%; CI95% 29.5 – 32.4).In low and middle income countries (LMIC), estimates from countries (China, Ghana, India, Mexico, Russia, and South Africa) included in the WHO Study on global AGEing and adult health (SAGE) Wave-1 (2007/10), found 21.9% (CI95%: 20.9; 22.9) of multimorbidity occurrence (≥2 diseases from a list from eight morbidities)[5]. This occurrence varied from 20.3% in China to 34.7% in Russia. In the present analysis, we used more diseases to

construct multimorbidity (22 against eight in SAGE study). Even so, the prevalence found was, virtually, equal to these other LMIC countries, except for Russia.

In Brazil, our occurrence findings were slightly lower than the result found in a paper with same database (-2 pp). Furthermore, the authors found three clusters which differ of our results (n=2) despite the resemblance of diseases grouping[12]. These variations are explained by the differences among diseases selected to measure multimorbidity and analysis steps to obtain the clusters. The standardization of multimorbidity operationalization is an urgent call to avoid loss of consistency in the development of the area [4]. Comparing with geographically located Brazilian results, our prevalence were lower than frequencies found in a Southern Brazilian city (29.1%; CI95%: 27.1; 31.1 for ≥2 morbidities, and 14.3 %; CI95%: 12.8; 15.8 for ≥3 morbidities) despite the higher number of morbidities included in this study [10]. The difference observed may be attributed to socioeconomic characteristics of Brazilian states. The states further South presented more development, wealth (both income and schooling) and higher life expectancy compared to other states [13] which tend to increase the occurrence of multimorbidity at contextual level.

In terms of socio-demographic characteristics, females and older adults presented more multimorbidity in all Brazilian regions as found in previous Brazilian [10 11] and international studies [26 27]. Women tend to use health services more and to live longer than males, these being factors which explain part of the higher frequency in this group. Survivors older adults tend to be exposed to more physiological damages in lifetime that contribute to chronic disease incidence [28]. In the same way, individuals who had partners had higher multimorbidity except to Central Western residents. The association between marital status should be more understanding through studies which include cultural assessment and its impact on chronic diseases development and diagnosis. One explanation is related to the fact

that individuals with partner tend to use more health services increasing the probability of medical diagnosis [29].

Regarding socioeconomic variables at individual level, our results follow the pattern found in overall analysis of a worldwide study [27] and LMIC included in the SAGE study. Multimorbidity and its factors was not associated with wealth quintiles but presented association with education [5] regardless Brazilian regions. In the present analysis, the middle wealth quintile strata and their clusters present more multimorbidity whilst showing a negative dose-response relationship with education. These results may be explained by a strong relationship between educational attainment and all aspects of healthier life including those mainly related to better awareness of chronic disease risk factors [30 31]. Education level seems to be a more adequate socioeconomic indicator to evaluate multimorbidity inequalities due to its worldwide association with poor health outcomes and longevity, and the persistent effect overtime [30]. Except for the early effect of childhood health status on education [32 33], chronic diseases in adult life tend to increase the risk of poverty (wealth index) [34] but the effect on education tend to be less relevant since education is usually achieved is early life

Having private health plans was associated with multimorbidity and its factors, except to Central Western and Southern. This may be explained, by the relationship with self-reported diagnosis (a fundamental characteristic of the outcome). Individuals with health plans tend to use health services more frequently regardless the presence of chronic conditions[35 36] thus affording more diagnosis.

Individuals who lived in urban areas presented more multiple diseases. This was similar to results found in the adult population in South Africa [37] and Catalonia (Spain)[38]. In spite

of little Brazilian evidence on the topic, as well as the social, cultural and environment differences between rural-urban residents, people from rural areas had more difficulty in accessing health services in Brazil [39] which may explain partially the differences between rural and urban residents in our results of the occurrence of self-reported medical diagnosis of multiple diseases.

The state-level differences observed reveal a paradoxical association. Instead of individual inequalities are pro-rich, state-level differences are pro-poor. These results might be explained by demographic differences between states in Brazil which may not be fully adjusted with individual demographic variables included in the analysis. Low income and low education in Brazilian states are concentrated in North and Northeast regions and show the poorest health-related indicators[13]. The states further south (*Rio Grande do Sul* - 27.2% and *Santa Catarina* - 27.1%) present greater multimorbidity frequencies.

The two factors (cardiometabolic and respiratory/mental/muscle-skeletal) found have some similarity to recent evidence [40 41] mainly related to cardiometabolic patterns. The respiratory/mental/muscle-skeletal data found was similar to results found in a worldwide study of people aged 50 or over [42]. The majority of studies, especially with adult populations, found two or three patterns of diseases. These combinations of diseases suggest possible causal relationship between diseases or their risk factors [20]. The cardiometabolic pattern showed a more well know relationship between diseases. On the other hand, the relationship between respiratory, mental and muscle-skeletal disorders is less understood. The concomitant occurrence of these diseases is well described [43] but understanding the biological plausibility of causal relationships will be a challenge for new studies. As a first step, more detailed and specific information about onset of diseases will be needed. At the same time, the use of approaches related to network analysis can be useful for a better

understanding of causal relationships [44]. Even so, the results presented here may contribute to the inclusion of recommendations in Brazilian clinical guidelines about the relationship with chronic conditions, as well as to designing interventions/public policies considering the presence of multiple diseases in the same individual.

Some limitations of the study should be addressed. With the exception of depression, all the other morbidities were evaluated by self-reporting. This may provide a misclassification bias even though self-reported diagnosis is considered an adequate and common source of information used in population-based studies on multimorbidity [4 45 46]. Nevertheless, the lack of adequate information about diagnosis, including longitudinal information, limits the causal inference related to concomitant diseases expressed in factorial analysis. Furthermore, we are not able to evaluate the contextual determinants at neighborhood level which may produce more complete associations with state-level differences.

The absolute and relative number of Brazilian individuals with multimorbidity was high. Addressing the complexity of multiple disease management for at least 19 million people will be a challenge for the health system. The clusters of diseases identified might contribute to strategies for the prevention and clinical care of these diseases. State and individual-level inequalities increase the problem reinforcing the need of a wide lens to organize health services and to decrease the inequities among the Brazilian population.

Author contributions

BPN designed the article, obtained and analyzes the data, drafted the first version and revised the manuscript. ADPCF and FACF analyzed the data, and drafted and revised the manuscript. SP, DS, TRF, TNM, ET and LAF drafted and revised the manuscript. SBR designed the article, drafted and revised the manuscript. All authors approved the final version of the manuscript.

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Tables and figures

Table 1. Description of the sample and multimorbidity frequency. Brazil, 2013.

Variables	n	%	Multimorbidity ≥2		Multimorbidity ≥3	
			%	95%CI	%	95%CI
Sex						
Male	25,920	44.9	17.5	16.6; 18.3	7.2	6.6; 7.8
Female	34,282	55.1	26.1	25.2; 27.0	12.6	12.0; 13.3
Age (in years)						
18 to 29	14,321	24.3	4.9	4.2; 5.6	1.2	0.9; 1.5
30 to 39	14,269	21.0	10.6	9.6; 11.5	2.8	2.3; 3.3
40 to 49	11,405	18.8	20.8	19.5; 22.1	7.8	7.0; 8.6
50 to 59	9,030	16.8	32.9	31.2; 34.6	15.5	14.3; 16.8
60 to 69	6,238	10.8	46.3	44.1; 48.6	24.7	22.8; 26.6
70 to 79	3,441	5.7	52.2	49.2; 55.2	30.9	28.0; 33.9
80 or more	1,498	2.6	52.8	48.6; 57.0	30.6	26.5; 34.7
Skin color*						
White	24,106	47.8	24.3	23.3; 25.4	11.6	10.8; 12.3
Black	5,631	9.2	22.2	20.2; 24.2	10.3	8.9; 11.6
Brown	29,512	41.7	19.8	18.9; 20.6	8.6	8.1; 9.2
Marital status						
Without partner	25,680	38.4	20.6	19.7; 21.5	9.9	9.3; 10.6
With partner	34,522	61.6	23.2	22.4; 24.1	10.4	9.7; 11.0
Schooling (in years)						
0	9,434	13.9	33.2	31.4; 35.0	16.3	14.9; 17.7
1-8	14,649	25.7	30.0	28.6; 31.4	16.1	14.9; 17.2
8-11	9,215	15.3	17.9	16.5; 19.3	7.5	6.5; 8.4
≥12	26,904	45.2	15.8	15.0; 16.7	5.9	5.4; 6.5
Wealth index (in quintiles)						
1º (High)	10,153	22.3	22.0	20.5; 23.6	9.3	8.3; 10.4
2º	11,531	22.4	22.3	21.0; 23.6	10.5	9.5; 11.5
3º	11,621	19.5	23.1	21.8; 24.4	10.6	9.7; 11.5
4º	14,380	21.0	22.2	20.9; 23.5	10.6	9.7; 11.6
5º (Low)	12,517	14.7	21.3	19.9; 22.7	9.9	8.9; 10.9
Private health plan						
No	43,834	69.4	21.1	20.3; 21.9	9.8	9.3; 10.4
Yes	16,368	30.6	24.8	23.5; 26.1	11.0	10.1; 12.0
Geographical area						
Urban	49,245	86.5	22.8	22.0; 23.5	10.5	10.0; 11.1
Rural	10,957	13.5	18.6	17.2; 20.0	8.0	7.1; 8.8
State-level education						

High	22,382	37.2	24.7	23.7; 25.7	11.7	10.9; 12.4
Middle	19,515	32.4	20.1	18.6; 21.7	9.3	8.3; 10.4
Low	18,305	30.4	19.0	18.0; 20.1	8.0	7.3; 8.6
State-level income						
High	21,683	36.0	24.6	23.6; 25.7	11.6	10.8; 12.3
Middle	18,087	30.0	21.8	20.2; 23.3	10.5	9.5; 11.6
Low	20,432	33.9	18.2	17.2; 19.2	7.5	6.9; 8.1
Total	60,202	100.0	22.2	21.5; 22.9	10.2	9.7; 10.7

Table 2. Adjusted multilevel models of multimorbidity with independent variables. Brazil, 2013.

Variables	Multimorbidity (≥2)						Multimorbidity (≥3)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%	OR	CI95%
Sex (ref: male)												
Female	**1.84**	**1.76; 1.94**	**1.85**	**1.77; 1.94**	**1.85**	**1.77; 1.94**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.08**	**1.95**	**1.83; 2.09**
Age (in years)	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**	**1.06**	**1.06; 1.06**
Skin color* (ref: White)												
Black	1.07	0.99; 1.16	1.08	0.99; 1.17	1.08	0.99; 1.17	1.09	0.98; 1.21	1.09	0.98; 1.21	1.09	0.98; 1.21
Brown	1.01	0.96; 1.06	1.01	0.96; 1.07	1.01	0.96; 1.07	0.97	0.91; 1.04	0.97	0.91; 1.04	0.97	0.91; 1.04
Marital status (ref: Without partner)												
With partner	**1.13**	**1.08; 1.18**	**1.13**	**1.08; 1.19**	**1.13**	**1.08; 1.19**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**	**1.17**	**1.09; 1.24**
Schooling (in years) [#] (ref: ≥12)												
8-11	**1.19**	**1.11; 1.28**	**1.19**	**1.10; 1.28**	**1.19**	**1.10; 1.28**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**	**1.22**	**1.10; 1.35**
1-8	**1.41**	**1.33; 1.51**	**1.41**	**1.33; 1.50**	**1.41**	**1.33; 1.50**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**	**1.57**	**1.44; 1.71**
0	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.34**	**1.24; 1.44**	**1.41**	**1.27; 1.56**	**1.41**	**1.28; 1.56**	**1.41**	**1.28; 1.56**
Wealth index (in quintiles) (ref: High)												
2º	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.12**	**1.04; 1.20**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**	**1.15**	**1.04; 1.28**
3º	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.21**	**1.12; 1.31**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**	**1.19**	**1.07; 1.33**
4º	1.05	0.96; 1.14	1.05	0.97; 1.14	1.05	0.97; 1.14	1.09	0.98; 1.22	1.10	0.98; 1.23	1.10	0.98; 1.23
5º (Low)	0.91	0.83; 1.00	0.92	0.84; 1.01	0.92	0.84; 1.01	0.95	0.84; 1.08	0.95	0.84; 1.08	0.95	0.84; 1.08
Private health plan (ref: no)												
Yes	**1.15**	**1.08; 1.21**	**1.15**	**1.08; 1.20**	**1.15**	**1.08; 1.20**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**	**1.09**	**1.01; 1.18**
Geographical area (ref: urban)												
Rural	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.86**	**0.80; 0.92**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**	**0.78**	**0.71; 0.86**
State-level education (ref: High)												
Middle			**0.82**	**0.71; 0.94**					**0.76**	**0.64; 0.90**		
Low			**0.83**	**0.72; 0.96**					**0.76**	**0.64; 0.90**		
State-level income (ref: High)												
Middle					0.89	0.77; 1.04					0.88	0.73; 1.05
Low					**0.82**	**0.71; 0.95**					**0.75**	**0.63; 0.89**

483 Table 3. Adjusted multilevel models of multimorbidity with independent variables stratified by region. Brazil, 2013.

Variables	Northern region		Northeastern region		Central Western region		Southeastern region		Southern region	
	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%	MM (≥2) OR CI95%	MM (≥3) OR CI95%
Sex (ref: male)										
Female	**1.81** **1.62; 2.02**	**2.06** **1.75; 2.43**	**1.96** **1.8; 2.14**	**2.08** **1.84; 2.36**	**2.22** **1.94; 2.54**	**2.37** **1.97; 2.86**	**1.62** **1.48; 1.78**	**1.61** **1.43; 1.82**	**1.84** **1.63; 2.08**	**2.04** **1.73; 2.39**
Age (in years)	**1.05** **1.05; 1.06**	**1.06** **1.05; 1.06**	**1.06** **1.06; 1.06**	**1.06** **1.06; 1.06**	**1.07** **1.06; 1.07**	**1.07** **1.06; 1.07**	**1.05** **1.05; 1.06**	**1.05** **1.05; 1.06**	**1.06** **1.05; 1.06**	**1.06** **1.06; 1.07**
Marital status (ref: Without partner)										
With partner	**1.13** **1.02; 1.27**	**1.17** **1; 1.38**	**1.16** **1.07; 1.27**	**1.23** **1.09; 1.39**	1.00 0.87; 1.14	0.93 0.78; 1.11	**1.15** **1.05; 1.26**	**1.22** **1.08; 1.38**	**1.16** **1.02; 1.32**	**1.19** **1.01; 1.4**
Skin color* (ref: White)										
Black	1.01 0.82; 1.23	1.06 0.79; 1.42	1.12 0.97; 1.3	1.14 0.94; 1.39	0.94 0.74; 1.21	0.89 0.63; 1.26	1.11 0.96; 1.29	1.15 0.95; 1.4	1.00 0.76; 1.31	0.98 0.7; 1.38
Brown	0.92 0.81; 1.04	0.92 0.76; 1.1	0.96 0.87; 1.05	0.93 0.81; 1.05	1.13 0.98; 1.29	1.14 0.95; 1.36	1.07 0.97; 1.18	1.02 0.89; 1.16	1.08 0.91; 1.27	0.88 0.71; 1.09
Schooling (in years) [#] (ref: more educated)										
III	1.17 0.99; 1.39	1.12 0.86; 1.47	1.10 0.95; 1.28	0.95 0.76; 1.18	1.16 0.94; 1.42	1.32 0.99; 1.75	**1.35** **1.18; 1.55**	**1.47** **1.22; 1.78**	1.12 0.94; 1.35	1.27 0.99; 1.62
II	**1.23** **1.05; 1.44**	**1.36** **1.08; 1.71**	**1.33** **1.18; 1.51**	**1.35** **1.14; 1.6**	**1.33** **1.11; 1.59**	**1.32** **1.03; 1.68**	**1.65** **1.46; 1.86**	**1.89** **1.61; 2.22**	**1.43** **1.22; 1.68**	**1.73** **1.41; 2.13**
I (less educated)	**1.32** **1.12; 1.55**	**1.48** **1.16; 1.88**	**1.38** **1.21; 1.58**	**1.36** **1.13; 1.65**	1.17 0.94; 1.46	1.25 0.94; 1.68	**1.43** **1.22; 1.67**	**1.40** **1.14; 1.71**	1.19 0.97; 1.47	**1.46** **1.12; 1.89**
Wealth index (in quintiles) (ref: High)										
2º	1.03 0.83; 1.29	0.92 0.67; 1.27	1.07 0.91; 1.26	1.21 0.96; 1.52	**1.29** **1.05; 1.58**	1.17 0.89; 1.55	1.03 0.90; 1.18	1.09 0.91; 1.3	**1.22** **1.04; 1.44**	1.25 1.00; 1.57
3º	1.21 0.98; 1.51	0.98 0.71; 1.34	**1.26** **1.07; 1.48**	**1.40** **1.11; 1.76**	1.19 0.95; 1.48	1.10 0.82; 1.48	1.02 0.89; 1.18	1.05 0.87; 1.27	**1.42** **1.18; 1.7**	**1.33** **1.05; 1.69**
4º	0.90 0.72; 1.12	0.82 0.60; 1.11	1.07 0.91; 1.26	1.22 0.97; 1.53	1.13 0.9; 1.42	1.18 0.88; 1.59	0.96 0.82; 1.12	0.98 0.79; 1.20	**1.34** **1.09; 1.66**	1.30 1.00; 1.7
5º (Low)	0.80 0.64; 1.01	0.74 0.53; 1.03	0.93 0.78; 1.12	0.97 0.76; 1.25	1.05 0.80; 1.36	1.16 0.83; 1.62	0.94 0.77; 1.14	1.13 0.88; 1.45	0.92 0.71; 1.20	0.85 0.61; 1.19

Private health plan (ref: no)										
Yes	1.15	**1.29**	**1.23**	**1.22**	1.15	1.16	**1.12**	1.05	1.10	0.91
	0.98; 1.35	**1.02; 1.61**	**1.09; 1.39**	**1.04; 1.44**	0.99; 1.34	0.95; 1.41	**1.01; 1.24**	0.92; 1.2	0.96; 1.25	0.77; 1.09
Geographical área (ref: urban)										
Rural	0.89	**0.76**	**0.84**	**0.75**	0.91	0.85	0.88	0.82	**0.82**	0.83
	0.77; 1.03	**0.61; 0.94**	**0.75; 0.94**	**0.64; 0.88**	0.75; 1.11	0.65; 1.11	0.76; 1.02	0.67; 1.00	**0.68; 0.97**	0.67; 1.04

Note: MM = Multimorbidity

Table 4. Adjusted multilevel models of patterns of diseases (factors) with independent variables. Brazil, 2013.

Variables	Factor 1 (Cardiometabolic)						Factor 2 (Respiratory/mental/ muscle-skeletal)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%	β	CI95%
Sex (ref: male)												
Female	**.024**	**.022; .026**	**.024**	**.022; .026**	**.024**	**.022; .026**	**.038**	**.036; .040**	**.038**	**.036; .040**	**.038**	**.036; .040**
Age (in years)	**.004**	**.004; .004**	**.004**	**.004; .004**	**.004**	**.004; .004**	**.001**	**.001; .001**	**.001**	**.001; .001**	**.001**	**.001; .001**
Skin color* (ref: White)												
Black	**.007**	**.003; .010**	**.007**	**.003; .010**	**.007**	**.003; .010**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**	**-.009**	**-.013; -.005**
Brown	.001	-.001; .004	.002	-.001; .004	.002	-.001; .004	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**	**-.004**	**-.006; -.001**
Marital status (ref: Without partner)												
With partner	.000	-.002; .002	.000	-.002; .002	.000	-.002; .002	**-.005**	**-.007; -.002**	**-.005**	**-.007; -.003**	**-.005**	**-.007; -.003**
Schooling (in years) [#] (ref: ≥12)												
8-11	**.013**	**.010; .016**	**.013**	**.010; .016**	**.013**	**.010; .016**	**.004**	**.001; .008**	**.005**	**.002; .008**	**.005**	**.002; .008**
1-8	**.021**	**.018; .023**	**.021**	**.018; .023**	**.021**	**.018; .023**	**.011**	**.008; .014**	**.011**	**.008; .014**	**.011**	**.008; .014**
0	**.014**	**.010; .017**	**.014**	**.010; .017**	**.014**	**.010; .017**	.001	-.003; .004	.001	-.003; .005	.001	-.003; .005
Wealth index (in quintiles) (ref: High)												
2º	**.007**	**.004; .010**	**.007**	**.004; .010**	**.007**	**.004; .010**	**.005**	**.001; .008**	**.005**	**.001; .008**	**.005**	**.001; .008**
3º	**.009**	**.006; .013**	**.009**	**.006; .013**	**.009**	**.006; .013**	**.010**	**.006; .014**	**.010**	**.006; .014**	**.010**	**.006; .014**
4º	**.006**	**.002; .009**	**.006**	**.002; .009**	**.006**	**.002; .009**	.004	.000; .008	.004	.000; .008	.004	.000; .008
5º (Low)	-.003	-.007; .001	-.003	-.007; .001	-.003	-.007; .001	.001	-.004; .005	.001	-.004; .005	.001	-.004; .005
Private health plan (ref: no)												
Yes	**.006**	**.004; .009**	**.006**	**.004; .009**	**.006**	**.004; .009**	**.007**	**.005; .010**	**.007**	**.005; .010**	**.007**	**.005; .010**
Geographical area (ref: urban)												
Rural	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	**-.008**	**-.011; -.005**	-.002	-.005; .002	-.002	-.005; .002	-.002	-.005; .002
State-level education (ref: High)												
Middle			**-.010**	**-.016; -.004**					**-.016**	**-.027; -.005**		
Low			**-.008**	**-.015; -.002**					**-.018**	**-.029; -.006**		
State-level income (ref: High)												
Middle					-.006	-.012; .001					-.011	-.022; .001
Low					**-.009**	**-.016; -.003**					**-.017**	**-.028; -.006**

Table 5. Adjusted multilevel models of multimorbidity factors with independent variables stratified by region. Brazil, 2013.

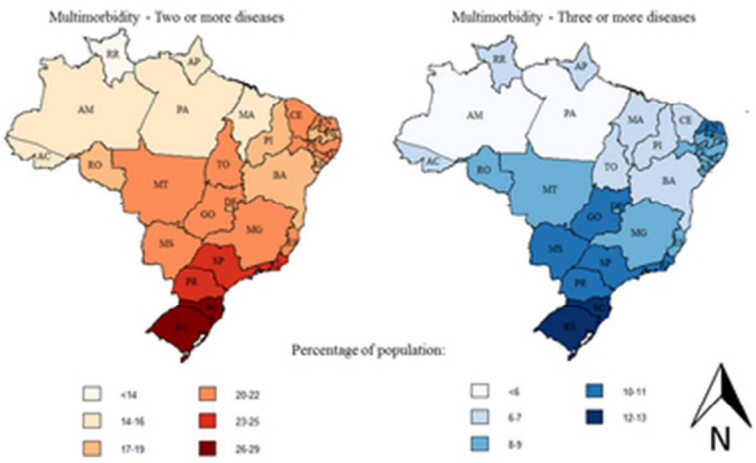
Variables	Northern region		Northeastern region		Central Western region		Southeastern region		Southern region	
	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%	Factor 1 β CI95%	Factor 2 β CI95%
Sex (ref: male)										
Female	**0.022**	**0.023**	**0.027**	**0.030**	**0.029**	**0.050**	**0.020**	**0.041**	**0.023**	**0.061**
	0.018; 0.026	**0.019; 0.027**	**0.023; 0.03**	**0.027; 0.034**	**0.023; 0.034**	**0.044; 0.056**	**0.015; 0.024**	**0.036; 0.045**	**0.017; 0.03**	**0.053; 0.069**
Age (in years)	**0.003**	**0.001**	**0.004**	**0.001**	**0.004**	**0.001**	**0.004**	**0.001**	**0.004**	**0.002**
	0.003; 0.003	**0.001; 0.001**	**0.003; 0.004**	**0.001; 0.001**	**0.004; 0.004**	**0.001; 0.002**	**0.004; 0.004**	**0.001; 0.001**	**0.004; 0.004**	**0.001; 0.002**
Marital status (ref: Without partner)										
With partner	0.001	-0.002	0.000	-0.002	**-0.007**	**-0.013**	0.001	-0.005	0.002	**-0.010**
	-0.003; 0.005	-0.006; 0.003	-0.003; 0.004	-0.005; 0.002	**-0.013; -0.002**	**-0.02; -0.007**	-0.003; 0.005	-0.010; 0.000	-0.004; 0.009	**-0.018; -0.002**
Skin color* (ref: White)										
Black	0.005	-0.007	**0.007**	-0.003	-0.001	**-0.021**	**0.008**	**-0.011**	0.013	-0.018
	-0.002; 0.013	-0.015; 0.001	**0.001; 0.013**	-0.01; 0.003	-0.011; 0.009	**-0.033; -0.01**	**0.001; 0.016**	**-0.02; -0.003**	-0.001; 0.026	-0.036; 0.000
Brown	-0.002	**-0.007**	-0.001	-0.003	0.004	-0.003	0.004	-0.002	0.005	0.004
	-0.007; 0.002	**-0.012; -0.002**	-0.005; 0.003	-0.008; 0.001	-0.001; 0.01	-0.010; 0.004	-0.001; 0.009	-0.008; 0.003	-0.003; 0.014	-0.007; 0.015
Schooling (in years) [#] (ref: more educated)										
III	0.006	**0.007**	**0.011**	0.000	**0.012**	-0.001	**0.016**	0.007	**0.019**	0.010
	0.000; 0.011	**0.001; 0.013**	**0.006; 0.017**	-0.006; 0.006	**0.004; 0.02**	-0.011; 0.008	**0.010; 0.023**	0.000; 0.014	**0.01; 0.028**	-0.002; 0.021
II	**0.009**	0.005	**0.015**	**0.006**	**0.016**	-0.001	**0.029**	**0.019**	**0.037**	**0.020**
	0.003; 0.014	-0.001; 0.011	**0.010; 0.020**	**0.001; 0.012**	**0.009; 0.024**	-0.01; 0.008	**0.023; 0.035**	**0.013; 0.026**	**0.028; 0.046**	**0.009; 0.031**
I (less educated)	**0.014**	**0.008**	**0.010**	0.002	**0.015**	-0.009	**0.022**	-0.002	**0.016**	-0.005
	0.008; 0.02	**0.001; 0.014**	**0.004; 0.015**	-0.004; 0.008	**0.005; 0.025**	-0.021; 0.002	**0.014; 0.03**	-0.011; 0.007	**0.004; 0.027**	-0.02; 0.01
Wealth index (in quintiles) (ref: High)										
2º	0.005	0.005	0.005	0.002	0.008	0.004	0.004	-0.003	**0.011**	**0.017**
	-0.003; 0.013	-0.004; 0.013	-0.002; 0.011	-0.005; 0.009	-0.001; 0.016	-0.005; 0.014	-0.002; 0.011	-0.01; 0.004	**0.003; 0.002**	**0.007; 0.028**
3º	**0.009**	0.004	**0.012**	**0.010**	0.002	0.002	0.004	0.002	**0.012**	**0.027**
	0.001; 0.017	-0.004; 0.013	**0.005; 0.018**	**0.003; 0.017**	-0.007; 0.011	-0.008; 0.013	-0.003; 0.011	-0.005; 0.01	**0.003; 0.021**	**0.015; 0.039**

4º	0.004	-0.001	0.005	0.004	0.005	0.005	0.003	-0.007	0.009	**0.019**
	-0.004; 0.011	-0.01; 0.007	-0.002; 0.011	-0.003; 0.011	-0.005; 0.014	-0.006; 0.016	-0.004; 0.011	-0.015; 0.001	-0.002; 0.02	**0.005; 0.033**
5º (Low)	-0.004	-0.009	-0.001	0.004	0.001	0.004	-0.006	-0.004	-0.012	0.012
	-0.012; 0.004	-0.017; 0.000	-0.009; 0.006	-0.003; 0.012	-0.010; 0.012	-0.008; 0.017	-0.015; 0.004	-0.015; 0.006	-0.026; 0.002	-0.006; 0.029
Private health plan (ref: no)										
Yes	**0.009**	**0.009**	**0.010**	**0.008**	0.007	**0.009**	0.002	**0.008**	0.005	0.001
	0.003; 0.015	**0.003; 0.016**	**0.006; 0.015**	**0.003; 0.013**	0.000; 0.013	**0.001; 0.016**	-0.003; 0.006	**0.002; 0.013**	-0.002; 0.012	-0.008; 0.01
Geographical área (ref: urban)										
Rural	**-0.007**	0.004	**-0.008**	**-0.006**	**-0.009**	**-0.001**	-0.007	**-0.010**	-0.008	0.009
	-0.012; -0.002	-0.002; 0.009	**-0.013;-0.004**	**-0.011;-0.001**	**-0.018; -0.001**	**-0.01; 0.009**	-0.014; 0.000	**-0.018;-0.001**	-0.017; 0.002	-0.003; 0.021

Note: Factor 1: cardiometabolic; factor 2: (Respiratory/mental/ muscle-skeletal)

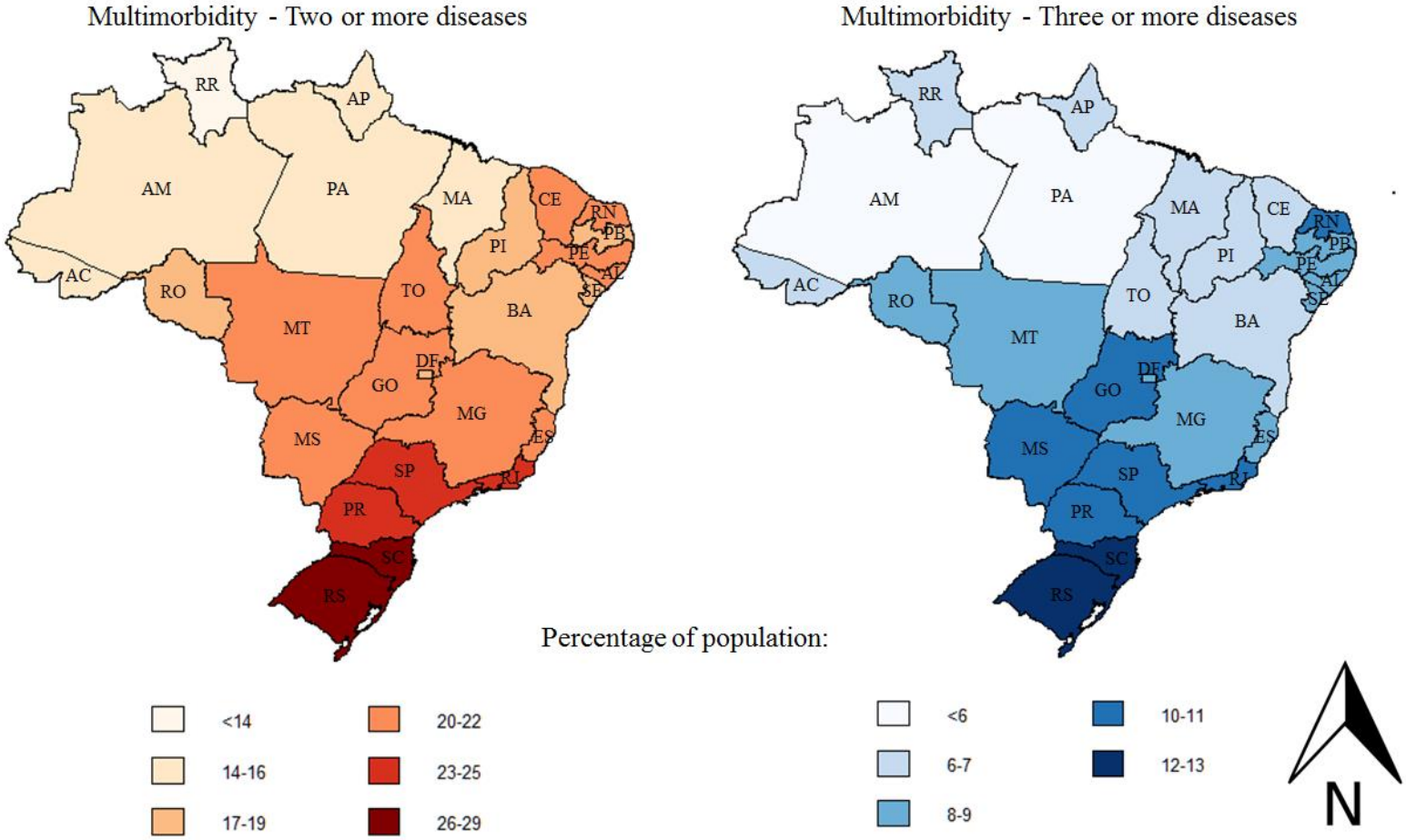
Supplementary table 1. Individual prevalence, duration and number of comorbidities for each morbidity evaluated. Brazil, 2013.

Morbidities	Individual prevalence		Duration of disease	Number of comorbidities
	%	(95%CI)	Mean (median; Q25-Q75)	Mean (median; Q25-Q75)
High Blood Pressure	22.3	21.7 - 23.0	13.1 (9; 3-18)	2.3 (2; 1-3)
Spinal column problem	19.0	18.3 - 19.7	14.7 (10; 4-21)	2.3 (2; 1-3)
Hypercholesterolemia	8.4	8.0 - 8.8	6.9 (3; 1-9)	2.3 (2; 1-3)
Arthritis/rheumatism	6.7	6.4 - 7.1	14.6 (10; 3-20)	3.0 (3; 2-4)
Diabetes	6.5	6.2 - 6.9	11.3 (6; 2-15)	2.9 (3; 2-4)
Asthma/wheezy bronchitis	4.4	4.1 - 4.8	25.1 (23; 13-35)	2.4 (2; 1-3)
Depression	4.2	3.9 - 4.5	-	2.9 (3; 2-4)
Work-related muscle-skeletal disorders	2.5	2.2 - 2.8	7.5 (5; 2-11)	2.5 (2; 1-3)
Cancer	1.9	1.7 - 2.2	8.5 (6; 2-13)	2.8 (2; 2-4)
Another heart disease	1.9	1.6 - 2.1	13.9 (9; 3-20)	3.1 (3; 2-4)
Stroke	1.6	1.4 - 1.8	10.2 (6; 2-13)	3.4 (3; 2-5)
Kidney problem	1.5	1.3 - 1.7	13.5 (9; 3-20)	3.2 (3; 2-4)
Heart attack	1.3	1.2 - 1.5	12.4 (7; 2-18)	4.0 (4; 3-5)
Heart failure	1.2	1.1 - 1.4	13.2 (8; 4-19)	4.0 (4; 2-5)
Bronchitis	1.0	0.8 - 1.1	23.2 (20; 9-32)	3.3 (3; 2-5)
Angina	0.8	0.7 - 0.9	15.5 (11; 5-21)	4.5 (4; 3-6)
Emphysema	0.5	0.4 - 0.6	14.9 (9; 3-18)	3.7 (3; 2-5)
Another lung disease	0.5	0.4 - 0.6	16.2 (12; 5-24)	2.8 (2; 1-4)
Bipolar disorder	0.4	0.3 - 0.5	11.3 (8; 4-16)	3.1 (3; 2-4)
Another mental disease	0.3	0.2 - 0.4	2.8 (2; 1-4)	2.5 (2; 1-3)
Schizophrenia	0.2	0.2 - 0.3	19.7 (19; 8-26)	2.7 (3; 2-3)
Obsessive Compulsive Disorder (OCD)	0.2	0.1 - 0.2	14.5 (12; 6-21)	3.4 (3; 2-4)



Multimorbidity frequency by Brazilian states. Brazil, 2013

39x21mm (300 x 300 DPI)


Multimorbidity - Two or more diseases
Multimorbidity - Three or more diseases
RR
AP
AM
PA
MA
CE
RN
PB
PI
PE
AL
SE
AC
RO
TO
BA
MT
DF
GO
MG
ES
MS
SP
RJ
PR
SC
RS
Percentage of population:
<14
14-16
17-19
20-22
23-25
26-29
<6
6-7
8-9
10-11
12-13
N

Supplementary table 2. Factor analysis. Brazil, 2013.

Morbidities	Factor 1	Factor 2
High Blood Pressure	0.77	
Heart attack	0.79	
Angina	0.68	
Heart failure	0.69	
Stroke	0.58	
Hypercholesterolemia	0.57	
Diabetes	0.62	
Arthritis/rheumatism	0.30	0.37
Spinal column problem		0.45
Asthma/wheezy bronchitis		0.57
COPD		0.63
Work-related muscle-skeletal disorders		0.45
Depression		0.46
Bipolar disorder		0.46
Kidney problem		0.31
Cancer	-	-
Eigenvalor	4.46	1.11
Explained variance %*	0.73 (0.69)	0.18 (0.47)
KMO	0.84	

*Before oblique rotation (after oblique rotation)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.