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- Accuracy of spirometry for detection of asthma

### Observational retrospective study:

- Cardiovascular emergencies in primary care: study of a large-scale telecardiology service

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- Non-invasive brain stimulation and computational models in post-stroke aphasic patients: single session of transcranial magnetic stimulation and transcranial direct current stimulation

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- What do Cochrane systematic reviews say about interventions for vitamin D supplementation?

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# Cardiovascular secondary prevention in primary care setting: an immediate necessity in Brazil and worldwide

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Cardiovascular diseases (CVD) such as coronary heart disease, stroke and peripheral arterial diseases are the leading causes of death worldwide.<sup>1</sup> The decline in age-adjusted mortality rates observed since the late 1960s was initially attributed partially to two concomitant factors. First, case-fatality rates have decreased due to better awareness of early symptoms and introduction of pre-hospital care, coronary care units, new drugs and surgical interventions. Second, reduction in the numbers of cigarettes smoked per day (smoking has been correlated with sudden death due to cardiac arrest) and lowering of very high blood pressures (hypertension has been correlated with massive hemorrhagic stroke) have played a significant role in reducing the risk of death due to cardiovascular diseases.<sup>2</sup> However, in contrast to assessments on mortality data, finding information about the incidence of CVDs is not an easy task. There are few empirical population-based studies, and extrapolation from mortality data with the aim of calculating incidence is insufficient.

We make the assumption that reductions in new-onset CVD cases are not occurring worldwide, or at least at the same pace observed for death rates. This assumption can be explained in terms of lifestyle changes that occurred during the 1990s. Primordial prevention (smoking bans, greater availability of healthy foods and encouragement of leisure-time physical activity) and more adequate primary prevention such as control of high blood pressure and high cholesterol became a reality.<sup>3</sup> However, a new factor rapidly spread worldwide: the epidemic of obesity and diabetes, which has increased the number of people prone to CVD events.<sup>4</sup>

If the rates of new-onset cardiovascular diseases do not decline, but the case-fatality rates drop, the prevalence of people with CVD should consequently increase. The confluence of these movements (declining lethality, stable incidence and rising obesity) has increased the numbers of survivors from myocardial infarction and stroke. These individuals, together with the pool of people with angina pectoris and peripheral artery disease, are responsible for the increase in cardiovascular disease prevalence rates. Data from the 2013 Brazilian National Health Survey and the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) revealed that higher prevalence of these conditions was strongly associated with lower socioeconomic status<sup>5-7</sup> (Table 1). Consequently, the prevalence of individuals who can be assigned to secondary prevention is growing mainly among the poorest.

Although the benefits of secondary prevention measures (lifestyle changes, blood pressure control and use of aspirin and statins) to reduce health-adverse cardiovascular events is undisputable,<sup>8</sup> these measures have not been adopted worldwide. In the Prospective Urban Rural Epidemiological (PURE) study, data on 153,996 adults with CVDs (aged 35-70 years) who were living in countries at different stages of economic development were analyzed. Comparing South America with North America/Europe, the rates of use of medications of proven effectiveness for people with coronary heart diseases (CHDs) or stroke were, respectively, 29% versus 52% for antiplatelet drugs; 58% versus 69% for blood pressure lowering agents; and 15% versus 52% for statins.<sup>9</sup> One explanation for these results is that neither outpatient cardiologic units, nor primary care facilities in South America have adopted trustworthy programs for secondary prevention as a public health policy.

**Table 1.** Prevalence ratios (and 95% confidence intervals) according to level of education, for heart diseases, angina and stroke from the 2013 Brazilian National Health Survey (NHS) and for peripheral artery disease from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)<sup>5-7</sup>

Education level	2013 NHS (n = 60,202)			ELSA-Brasil (n = 15,105)
	Heart disease	Angina pectoris	Stroke	Peripheral artery disease
Less than elementary	6.3 (5.7-6.9)	10.8 (10-11.5)	2.7 (2.4-3.1)	10.1 (9.5-0.6)
Elementary	3.1 (2.4-3.7)	7.5 (6.5-8.5)	0.8 (0.6-1.1)	8.8 (8.6-9.1)
High school	2.5 (2.0-2.9)	5.5 (4.9-6)	0.8 (0.8-1)	5.5 (5.4-5.7)
College	3.5 (2.5-4.4)	3.6 (2.9-14.4)	0.6 (0.6-0.8)	5.4 (5.3-5.5)

One challenge is to test how secondary prevention as provided by several guidelines should be practiced within primary care settings.<sup>8</sup> The problem of “secondary” (cardiovascular prevention) within the “primary” (care setting) is much more related to phraseology than to the capabilities and features of primary care units, including family health programs, which would undertake these measures immediately.

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# Clinical and epidemiological profile of tuberculosis in an urban area with high human development index in southeastern Brazil. Time series study

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## KEY WORDS:

Tuberculosis.  
Human development.  
Epidemiology.  
Risk factors.  
Acquired immunodeficiency syndrome.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** In the twenty-first century, tuberculosis remains a serious public health problem in Brazil. The aim here was to characterize tuberculosis in a municipality with a high human development index (HDI), based on clinical and epidemiological variables.

**DESIGN AND SETTING:** Epidemiological study with analysis of incidence that included 533 new cases of tuberculosis in the municipality of Araraquara, São Paulo, reported to the Brazilian Notifiable Diseases Information System (SINAN) between 2002 and 2011.

**METHODS:** To identify trends, this period was divided into two five-year periods (2002-2006 and 2007-2011). The incidence rates were compared using ratios and confidence intervals.

**RESULTS:** The incidence of tuberculosis was 26.82 cases per 100,000 inhabitants, and decreased by 22% between the two periods, which was statistically significant. Cases were more prevalent among men (72.61%) and among adults between 30 and 59 years of age with non-specialized professions and low education levels. There was a statistically significant reduction in cases among individuals over 50. The age group with highest incidence was 50-59 years in the first period and 30-39 years in the second. Total recovery occurred in more than 70%. There was a reduction in the number of diagnoses made within primary care and an increase within public hospital care between the two periods. The most common coinfections were AIDS and hepatitis C.

**CONCLUSIONS:** The incidence of tuberculosis in this municipality was lower than the national incidence, with a declining trend and a high cure rate, and the main coinfections were AIDS and hepatitis C.

## INTRODUCTION

Tuberculosis (TB) was declared a global emergency by the World Health Organization (WHO) in 1993. WHO has recommended directly observed treatment (short-course treatment), or DOTS, which focuses on detection, increasing the cure rate and decreasing patient withdrawal from treatment.<sup>1</sup> DOTS was quickly adopted by the Brazilian government, and resulted in improved care for TB carriers. Between 1995 and 2012, 56 million people were successfully treated in countries that adopted DOTS, with 22 million lives saved.<sup>2</sup>

In view of the improvement in the epidemiological situation of TB attained through DOTS, WHO adopted SDGs (Sustainable Development Goals) in 2015. These aim to reduce the incidence by 80% and mortality by 90%, by the year 2030. Furthermore, WHO adopted the End TB Strategy with the objective of reducing TB incidence by 90%, by 2035, in comparison with 2015 estimates.<sup>3</sup>

The numbers continue to astound: WHO estimates that one third of the world's population is infected with the tubercle bacillus. In 2010, 9.4 million new cases of TB were estimated, in addition to the existing 14 million cases. In that same year, there were 1.3 million deaths resulting from TB among people without AIDS worldwide. Another 380,000 deaths from TB occurred among HIV-positive patients.<sup>4</sup>

In Brazil, the numbers are slowly improving. In 1990, the national average was found to be 51.8 new TB cases per 100,000 inhabitants. This rate dropped to 38.4 in 2011.<sup>5</sup> TB mortality also decreased over this period, from 3.6 to 2.4 deaths per 100,000 inhabitants.<sup>5</sup> Because lack

of reporting negatively affects TB statistics in this country, these numbers may be underestimated.<sup>6,7</sup>

Early diagnosing of suspected cases and proper medication-based treatment for carriers of pulmonary tuberculosis are the most important measures for controlling the problem.<sup>8</sup> These measures are possible only with an active search for people who present the typical respiratory symptoms.<sup>9</sup> This type of control is no easy task, since presence of a cough for more than two weeks is not a symptom that is specific to TB; it is also absent in 5% of pulmonary TB cases among adults.<sup>10</sup>

Public and private preventive medical services have failed to define measures that allow early diagnosing of the disease.<sup>11</sup> Many studies have been conducted in different Brazilian cities and regions. The objective has often been to find the epidemiological patterns of TB in both the general population and in specific groups, such as children,<sup>12</sup> adolescents,<sup>13</sup> indigenous populations<sup>14</sup> and the prison population.<sup>15</sup>

According to WHO, Brazil is among the 30 countries of the world with the worst situation of TB cases and TB/HIV cases.<sup>3</sup> There were 81,137 notified TB cases in 2015, with approximately 5,500 deaths. The incidence was 41 per 100,000 inhabitants, and this is thought to correspond to 87% of the total number of cases, considering that the underreporting rate is estimated to be 13%. In relationship to multidrug-resistant TB, Brazil is in a comfortable situation compared with India and China, with incidence of 1.5% among all cases and 8% among retreatment cases.<sup>3</sup>

Knowledge of the epidemiological profile of TB is fundamental to the active search for cases and patients. It enables reduction of the times between the first symptoms, diagnosis and the start of supervised medication-based treatment.<sup>16,17</sup> Higher mortality rates are associated with late diagnoses, which in turn are the result of failures in the organization of primary healthcare systems.<sup>18</sup>

Tuberculosis is a problem associated with poverty, and most studies have been conducted in lower-income cities. The present study took a different approach: a municipality with a high human development index (HDI) was chosen. The HDI is an indicator comprising three aspects of human development: life expectancy, education and per capita income. This indicator has been adapted in Brazil from the global HDI due to unavailability of data in this country; it is referred to locally as the Municipal HDI.<sup>19</sup>

## OBJECTIVE

The objective of this study was to characterize the TB cases reported in a municipality in the southeastern region of Brazil, from 2002 to 2011, based on demographic and clinical variables, as well as on the type of healthcare institution where the diagnosis was made.

## METHODS

This was an epidemiological study on incidence that was exploratory and analytical in nature. It used different time series and

included all new cases of TB among residents of the municipality of Araraquara, São Paulo, that were reported to the Brazilian Notifiable Diseases Information System (SINAN) from 2002 to 2011. The study relied on this number of new TB cases reported during this period.

The municipality of Araraquara is located in the central region of the state of São Paulo. In 2010, it was found to have the 14<sup>th</sup> highest HDI in Brazil and the 8<sup>th</sup> highest in the state of São Paulo. Other municipalities in the region have similar characteristics. They include Ribeirão Preto, São Carlos and Rio Claro, all of which have more than 200,000 residents and relatively high HDIs. For this reason, this study of tuberculosis in Araraquara was expected to provide knowledge that might also aid other cities in the region.

The data used was obtained from the digital archives of the Special Healthcare Center of Araraquara (SESA), which is part of the University of São Paulo (USP). The name of the software is the Juarez System: the Integrated Public Health Information and Management System (referred to locally as Sistema Juarez). This database includes reports of TB cases among Araraquara residents. It has the same information as sent to SINAN and, in addition, it has information about the healthcare institution where the diagnosis was made. Population data was obtained from the Brazilian Institute for Geography and Statistics (IBGE) and was used to calculate the incidence rate of tuberculosis over the study period.<sup>20</sup>

The number of TB cases reported and population data from each year between 2002 and 2011 were collected. This period was analyzed firstly as a single unit and was then divided into two five-year periods (2002-2006 and 2007-2011) in order to identify epidemiological trends. The variables analyzed were sex, age, education level, occupation, TB location, healthcare institution where the diagnosis was made and presence of any other infectious diseases.

Statistical analysis was performed, and this included calculation of the incidence rates according to sex and age for each period. The two independent rates were compared using the ratio between them as point values (R) and 95% confidence intervals (95% CI).<sup>21</sup>

The results were displayed in tables. The criterion for deciding whether a significant difference existed between the rates in the five-year periods was to ascertain whether the confidence interval included the value 1. Thus, if this value was included, there was no significant difference. If the value 1 was not included, it could be said that the rates were significantly different.

## RESULTS

Between 2002 and 2011, 533 TB cases were reported among residents of the municipality of Araraquara, with an incidence of 26.82 cases per 100,000 inhabitants.

Through dividing the data into two periods of TB occurrence (2002-2006 and 2007-2011), decreased TB incidence was observed

in the second period. It decreased from 30.24 to 23.60 cases per 100,000 inhabitants, as shown in **Table 1**. In the period 2007-2011, TB incidence was 22% lower than in the period 2002-2006. The first period exhibited significantly greater incidence of TB than the second period:  $R = 1.28$  (95% CI: 1.06-1.50).

According to sex, the majority of the cases were found to be among males (72.61%), as detailed in **Table 2**. Among males (**Table 2**), the ratio between the two periods was  $R = 1.30$  (95% CI: 1.04-1.56), which was statistically significant. Different results were observed among females, for whom  $R = 1.22$  (95% CI: 0.82-1.62), which was non-significant. In addition to the predominance of male patients, a statistically significant difference in incidence was found between males and females within each of the periods. In relation to the periods 2002-2006 and 2007-2011, respectively,  $R = 2.90$  (95% CI: 2.80-3.00) and  $R = 2.73$  (95% CI: 1.97-3.49).

Regarding age-specific incidence, it was found that in the period 2002-2006, the greatest incidence of TB was among the group aged 50-59 years. On the other hand, in the period 2007-2011, the greatest incidence was among the group aged 30-39 years. Comparison between these two periods showed an equilibrium in the specific incidence ratios up to 39 years of age. Starting at 40 years of age, a decrease in incidence was found in the period 2007-2011, relative to the period 2002-2006. The incidence ratios organized according to age between the two periods (2002-2006 and 2007-2011) were found to be as follows:  $R = 1.58$  (95% CI: 0.98-2.18) for 40-49 years of age;  $R = 2.06$  (95% CI: 1.16-2.90) for 50-59 years of age; and  $R = 1.97$  (95% CI: 1.05-2.09) for 60 years of age and over. There was a significant decrease in incidence among residents aged 50 years and over.

Correlation of TB cases with educational level showed predominance of patients with only elementary school education, as can be seen in **Table 3**. These patients with elementary school education represented 62.33% of the cases in the period 2002-2006 and 57.68% of the cases in the period 2007-2011. These were followed by patients with complete or partial high school education, who represented 13.36% of the cases from 2002 to 2006 and 20.33% of the cases from 2007 to 2011. The third highest association was with illiterate patients, who represented 7.19% of the cases from 2002 to 2006 and 3.73% of the cases from 2007 to 2011, and these were followed by patients with tertiary education, who represented 5.48% of the cases from 2002 to 2006 and 4.56% of the cases from

**Table 1.** Number of reported cases of tuberculosis (n), population and incidence (per 100,000 inhabitants); Araraquara (SP), 2002-2006 and 2007-2011

Period	n	Population	Incidence
2002-2006	292	965,596	30.24
2007-2011	241	1,021,382	23.60

2007 to 2011. The proportions with lack of information regarding educational level were 11.64% and 13.69%, respectively regarding the start and end of the subjects' education.

Considering the type of institution where the tuberculosis diagnosis was made, most diagnoses between 2002 and 2011 were made within Brazil's public primary care network (**Table 3**). This network included primary care units (Unidades Básicas de Saúde, UBSs), family healthcare centers (Estratégia Saúde da Família, ESFs) and the School Healthcare Center of the state health department at the University of São Paulo (SESA). In the first period, 61.64% of the diagnoses were made within the primary care network, and this rate decreased to 49.97% in the second period. From 2002 to 2006, 21.23% of the diagnoses were made in urgent care centers or emergency rooms within private hospitals, and this proportion decreased to 12.45% in the second period. Also, 5.82% of the diagnoses were made in private doctors' offices and this rose to 8.71% in the period from 2007 to 2011. In the second period, the diagnoses made within the public primary care network represented nearly half of the total number of diagnoses (49.79%), followed by diagnoses made in public hospitals (17.01%), urgent care centers or emergency rooms within private hospitals (12.45%) and private doctors' offices (8.71%). The diagnoses made in public urgent care centers (UPAs), which are part of the Brazilian public healthcare system (Sistema Único de Saúde, SUS), represented only 1.71% of the diagnoses in the first period, and increased to 6.22% in the second period (**Table 3**).

The diagnostic methods used were clinical examination, bacilloscopy, sputum culture and X-ray, in all the healthcare institutions considered (UBSs, ESFs, SESA and public and private hospitals).

Regarding the type of conclusion from the treatment, cure rates of more than 70% were found in both periods. In the period 2002-2006, treatment conclusion due to death was more frequent

**Table 2.** Incidence (per 100,000 inhabitants) of tuberculosis according to sex and age; Araraquara (SP), 2002-2006 and 2007-2011

Explanatory variables	2002-2006	2007-2011
<b>Sex</b>		
Male	45.57	35.14
Female	15.72	12.85
<b>Age (years)</b>		
< 20	3.17	4.07
20-29	28.08	25.06
30-39	48.58	46.50
40-49	48.48	30.68
50-59	58.99	29.08
≥ 60	40.78	20.67

(13.01%) than in the period 2007-2011 (9.13%). Meanwhile, treatment conclusions resulting from patient withdrawal showed the opposite trend, with a higher rate among patients in the second period (4.15%) than in the first (2.74%).

The most common coinfections among TB patients were found to be AIDS and hepatitis C, as shown in Figure 1. The incidence of AIDS decreased by 23% among women, dropping from 34.62% in the period 2002-2006 to 26.47% in the period 2007-2011. On the other hand, among men, the co-prevalence of AIDS remained stable, with rates of 21.03% in the first period and 19.65% in the second period. Concomitant incidence of TB and hepatitis C increased by 83.46% among females: the rate jumped from 6.41% in the first period to 11.76% in the second period. Among males, concomitant occurrence of TB and hepatitis C decreased by 38.19%: from 12.15% in the period 2002-2006 to 7.51% in the period 2007-2011.

Regarding the location of TB, 94.8% of the cases were pulmonary, while the remaining cases were extrapulmonary, involving the pleura, lymph nodes and larynx, along with cases of tuberculous meningitis and TB in other locations. Only two reports were cases of multidrug-resistant tuberculosis.

In relation to the occupations of TB patients, “homemaker” and “inactive” (people whose incomes are inconsistent and often zero) were the most common, representing 12.57% and 18.57% of the cases, respectively. Professions requiring low levels of specialization, such as handyman, construction worker and construction worker’s

assistant, were also found, although less frequently. From 2002 to 2006, 2.74% of the patients were students and 2.40% reported having professions requiring higher education, such as doctors, lawyers and engineers.

## DISCUSSION

In a systematic review of the literature, TB was found to be associated with alcoholism, coinfection with HIV, low education level, marital status and low income.<sup>22</sup> The municipality of Araraquara is located in a region with high HDI and, for this reason, exhibits a unique epidemiological profile for TB. In some ways, however, its epidemiological profile is similar to that of other, less economically and socially developed regions of Brazil.

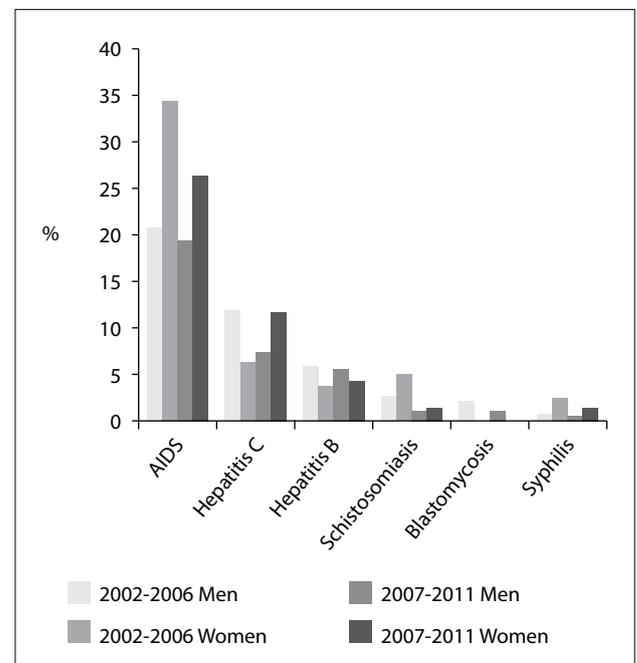
From 2002 to 2011, the TB incidence was 26.82 per 100,000 inhabitants. It decreased over the course of this period: from 30.24 per 100,000 inhabitants (2002-2006) to 23.60 per 100,000 inhabitants (2007-2011). These rates are lower than the overall incidence of TB in Brazil, which was 36.7 per 100,000 inhabitants from 2008 to 2011.<sup>23,24</sup> The decrease in the incidence of TB in Araraquara between the two five-year periods (2002-2006 and 2007-2011) was statistically significant. This finding demonstrates the trend towards real improvement in the status of this disease, which has resulted from changes to local social and sanitation conditions.

The predominance of males among TB patients (72.61% from 2002 to 2011) was consistent with the rates observed in other

**Table 3.** Patients’ educational status and type of institution where diagnosis was made, as number (n) and percentage (%); Araraquara (SP), 2002-2006 and 2007-2011

Explanatory variables	Period			
	2002-2006		2007-2011	
	n	%	n	%
<b>Educational status</b>				
Illiterate	21	7.19	9	3.73
Elementary school	182	62.33	139	57.68
High school	39	13.36	49	20.33
Tertiary	16	5.48	11	4.56
Unknown	34	11.64	33	13.69
<b>Type of institution</b>				
UBS/ESF	180	61.64	120	49.79
UPA	5	1.71	15	6.22
Private hospital	62	21.23	30	12.45
Public hospital	12	4.11	41	17.01
Private doctor’s office	17	5.82	21	8.71
Prison system	8	2.74	10	4.15
Unknown	8	2.74	4	1.66

UBS = primary care units (Unidade Básicas de Saúde, UBS); ESF = family healthcare centers (Estratégia Saúde da Família, ESF); UPA = urgent care centers (Unidade de Pronto-Atendimento, UPA).



**Figure 1.** Comorbidities among tuberculosis patients in relation to sex, as percentage (%); Araraquara (SP), 2002-2006 and 2007-2011.

locations, such as in the entire state of São Paulo<sup>25</sup> and the state of Minas Gerais, also in Brazil.<sup>26</sup> In Araraquara, this pattern was found to be stable, with no statistically significant changes over the course of the period studied. On the other hand, it was higher than what has been observed around the world (62%). However, it is possible that the estimated incidence in other countries could also have been underreported.<sup>3</sup>

The age range with the highest incidence of TB cases from 2002 to 2006 was 50 to 59 years of age. The average age among the cases was lower in the period 2007-2011, such that the greatest incidence was among patients between 30 and 39 years of age. In the second period (2007-2011), there was also a significant decrease in cases among residents 50 years of age and over. This predominance of new cases among adults in younger age groups was similar to the findings reported in studies at other locations and over the same period. In the city of Ribeirão Preto, which is located in the same region and has a socioeconomic profile similar to that of Araraquara, the maximum incidence in 2006 occurred among young adults (from 20 to 39 years of age).<sup>27</sup> Meanwhile, in the state of Minas Gerais, the residents most commonly affected between 2002 and 2009 were those between 20 and 49 years of age.<sup>26</sup>

Worldwide, 10% of TB cases were found among children under 14 years of age, which was concordant with Brazilian patterns in 2015.<sup>3</sup> In Araraquara, in the first period (2002-2006), 3% of the cases occurred among people under 19 years of age, and this rose to 4% in the second period (2007-2011). These values indicate the good social and health structure of the municipality studied. It is difficult to analyze this difference and it could be considered to be a limitation of this study.

In the two periods considered in this study, predominance of patients with low educational levels was found, such that two thirds of the patients reported only having elementary school education. This finding is similar to the reports found in a review of the literature on this topic.<sup>22</sup>

The type of conclusion from the treatment was considered, and cure rates greater than 70% were found in both periods. This was similar to the national average reported in 2013.<sup>28</sup> This consistency suggests that the higher HDI of the location studied has not been accompanied by greater efficacy among the measures taken to control TB.

Comparison of the locations of the diagnoses in the two periods showed some changes between the first and second periods. In the first period, 61.64% of the diagnoses were made within the primary care network (UBSs and ESFs), and this rate decreased to 49.97% in the second period. In the first period, the second most common location for the diagnosis was in private hospitals (21.23%). On the other hand, in the period 2007-2011, the second most common location for the diagnosis

was a state public hospital that was established at the beginning of the twenty-first century in a neighboring city; this hospital accounted for 17.01% of the diagnoses, and private hospital diagnoses decreased to 12.45%. This partial replacement of the primary care network by a public hospital is likely to be unique to this city. The public hospital in question is state-run; it is managed by the University of São Paulo. Because of the high quality of its services and its perceived prestige among local residents, this hospital became the preferred option for healthcare among the population. This hospital has also become a common destination for patients transferred by physicians within the public primary care network.

From 2002 to 2011, the most common locations for TB diagnoses within the city of São Paulo were hospitals and emergency rooms.<sup>29</sup> In the city of Ribeirão Preto, 57.4% of TB diagnoses were made within urgent care services in 2009;<sup>16</sup> similarly, in the city of São José do Rio Preto, 49.4% of the diagnoses in the same year were made within urgent care services.<sup>30</sup>

Coinfection with AIDS was found to have decreased by 23% among females when the two periods were compared: from 34.63% (2002-2006) to 26.47% (2007-2011). This coinfection with AIDS remained stable and lower among men, with rates of 21.03% in the first period and 19.65% in the second period. In Ribeirão Preto, the average rate of coinfection with AIDS for both sexes was 25% in 2006.<sup>27</sup> The numbers found in Araraquara and its region are very different from the national average, which was 10.1% (both sexes) in 2013; national rates among men are higher in general.<sup>28</sup> Although WHO recommends serological evaluation for HIV among TB patients, it is not done routinely in Araraquara, and only 55% of these patients worldwide underwent this evaluation in 2015.<sup>3</sup>

Only limited data on other comorbidities associated with TB are available in the literature, which makes additional comparisons difficult. In the present study, an 83.46% increase in TB-hepatitis C comorbidity was found among females, which reached a rate of 11.76% in the period 2007-2011. Among males, comparison between the two periods showed a 38.19% decrease in this comorbidity: from 12.15% to 7.51%. To understand these hepatitis C trends (the increase among women and the decrease among men), further study is required.

Occupations requiring less specialization (and, therefore, resulting in lower incomes) were found to be most common among the TB patients, who most commonly reported being homemakers or inactive (people whose income is often zero); or being construction workers or construction workers' assistants. This pattern is similar to what has been reported in the literature, such as in the municipality of Ribeirão Preto, where TB was found to be associated with low income.<sup>31</sup>

It should be mentioned that this study may present some limitations due to the high drop-out rate from TB treatment, and to

the lack of precise information on education. These occurrences may have compromised the findings regarding the epidemiological and clinical profile, with a greater lack of information in the second period.

It could be observed that, over the 10-year period, no population movements occurred in relation to immigration or wars, and there were also no changes in public health policies and healthcare systems that could have affected the rates of new TB cases, and consequently, the TB control programs. The literature shows that, in Brazil, tuberculosis is not a public health problem restricted to areas with less human or social development. The present study, conducted in a municipality with high HDI, demonstrates this fact. The similarities and differences between the municipality of Araraquara and the national trends in Brazil, in terms of epidemiological and clinical patterns, should serve as a basis for creation of public policies and disease control measures, even in municipalities with higher HDIs. The more general objectives are always faster diagnosis for the disease, increased cure rates and greater priority towards making resources available for social groups within which the disease is most frequent.

## CONCLUSIONS

The incidence of tuberculosis in this municipality was lower than the national incidence, with a declining trend and a high cure rate, and the main coinfections were AIDS and hepatitis C.

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# Methicillin-resistant *Staphylococcus aureus* in cystic fibrosis patients: do we need to care? A cohort study

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## KEY WORDS:

Cystic fibrosis.  
Methicillin-resistant *Staphylococcus aureus*.  
Tomography.  
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Body mass index.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** The prevalence of a variety of potentially pathogenic microorganisms in cystic fibrosis patients, such as methicillin-resistant *Staphylococcus aureus* (MRSA), has increased over the past decade. Given the increasing prevalence of MRSA and the few data available in the literature, better understanding of the clinical repercussions of colonization by this bacterium in cystic fibrosis patients becomes essential. This study aimed to evaluate the repercussions of chronic colonization by MRSA in cystic fibrosis patients.

**DESIGN AND SETTING:** Retrospective cohort study from January 2004 to December 2013 in a cystic fibrosis reference center.

**METHODS:** Each patient with cystic fibrosis was evaluated for nutritional status (body mass index, BMI, and BMI percentile), pulmonary function and tomographic abnormalities (modified Bhalla scores) at the time of chronic colonization by MRSA or methicillin-susceptible *Staphylococcus aureus* (MSSA) and throughout the study period.

**RESULTS:** Twenty pairs of patients were included. There were no significant differences between the groups regarding nutritional characteristics. Spirometric data showed a trend towards greater obstruction of the airways in patients with MRSA. Patients with MRSA presented greater structural damage to their lungs, demonstrated not only by the total Bhalla score but also by its parameters individually.

**CONCLUSIONS:** Patients colonized by MRSA presented greater functional and structural respiratory impairment at the time of chronic colonization. Disease progression was also faster in patients chronically colonized by MRSA than in those with MSSA. This was shown through comparisons that avoided possible confounding variables.

## INTRODUCTION

Bacterial respiratory infection starts early in cystic fibrosis (CF) patients and *Staphylococcus aureus* (*S. aureus*) and *Haemophilus influenzae* are the main pathogens in young patients.<sup>1</sup> Increasing life expectancy has led to higher prevalence of new pathogens in these patients,<sup>2</sup> especially methicillin-resistant *S. aureus* (MRSA).<sup>3</sup> The prevalence of MRSA infection in CF patients in the United States rose from 2% in 2001 to 26.5% in 2014.<sup>4</sup> While *Pseudomonas aeruginosa* and the *Burkholderia cepacia* complex are classically associated with respiratory deterioration and worsening of life expectancy, the clinical impact of MRSA colonization is not so clear.<sup>5</sup>

Since the clinical course of CF respiratory disease varies between patients, information that clearly depicts the conditions of the respiratory system and progression of pulmonary structural lesions is needed, especially among patients infected by MRSA. Nutritional status directly influences multisystemic involvement among CF patients and it has been considered that body mass index (BMI) is the most important parameter to be monitored. The association of better nutritional status with improved lung function is well documented and poor nutritional status with lower BMI is a risk factor for accelerated decline in lung function.<sup>6</sup>

Premature deaths continue to result directly or indirectly from loss of lung function. Therefore, spirometric measurements are important surrogate measures of disease progression, particularly forced expiratory volume in the first second (FEV<sub>1</sub>%) and predicted forced vital capacity (FVC%).<sup>6</sup>

High-resolution computed tomography (HRCT) of the chest is a specific imaging method that can be used to evaluate early airway disease and parenchymal lesions. Furthermore, it has high

sensitivity and specificity for diagnosing lung injury and also allows better qualitative description of respiratory impairment.<sup>7,8</sup> HRCT results are presented as graphical images, which may be converted to score values that are useful for evaluating disease severity. Since the first proposal for creation of a computed tomography scoring system to quantify structural abnormalities in CF patients,<sup>9</sup> other scoring systems have been described and been shown to be reproducible and comparable.<sup>7</sup> The modified Bhalla score<sup>10</sup> was shown to be reproducible and reliable, regardless of the severity of the lesions, which suggests that it is applicable in clinical practice for CF cases.<sup>11</sup>

## OBJECTIVE

The aim of this study was to evaluate the clinical and tomographic impact of chronic MRSA infection in CF patients and compare these data with those from a group of individuals chronically colonized by methicillin-susceptible *S. aureus* (MSSA).

## METHODS

This retrospective cohort study was conducted in the main CF center for children and adolescents in Rio de Janeiro, Brazil: the Fernandes Figueira National Institute for Women's, Children's and Adolescents' Health (Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Oswaldo Cruz Foundation, Ministry of Health), from January 2004 to December 2013. Approval was obtained from this institution's ethics committee (number CAAE 27902814.9.0000.5269).

In this institution, respiratory secretions (either sputum or throat swabs in the case of children under two years of age who were unable to provide sputum samples) were cultured in accordance with standardized protocols that had been established for CF patients. This was done on a three-monthly basis throughout the study.<sup>12</sup>

The inclusion criteria for the patients were that they needed to have a CF diagnosis in accordance with the Cystic Fibrosis Foundation consensus;<sup>13,14</sup> undergo regular clinical and laboratory follow-up during the study period; and present chronic colonization with *S. aureus* (MSSA or MRSA) in respiratory secretions (three or more isolations over a 12-month period).<sup>15,16</sup> All patients that met eligibility criteria were consecutively included in the study and their data was recovered from medical records. Subjects who presented no respiratory colonization or were colonized with *B. cepacia* complex or presented intermittent colonization with *S. aureus* (less than three isolations over a 12-month period) were excluded from the study. No anti-staphylococcal prophylaxis is regularly used at this center. After the first isolation of MRSA (i.e. before chronic colonization), the patients underwent a course of antibiotics that included two weeks of rifampicin and trimethoprim-sulfamethoxazole and five days of topical mupirocin.

Each of the 20 chronic MRSA patients was matched with a control (chronic MSSA CF patient) in accordance with the following

criteria: gender, age, time of chronic colonization with *S. aureus* ( $\pm 1$  year) and chronic coinfection with *P. aeruginosa*.<sup>17</sup>

For each patient, medical record data were evaluated, including gender, age and pancreatic insufficiency (fecal fat or fecal elastase or need for exogenous replacement enzymes). The clinical outcome of each patient was also evaluated, considering the following parameters: BMI and BMI percentile for children over the age of two years, spirometric parameters such as predicted forced expiratory volume in the first minute (FEV<sub>1</sub>%) and predicted forced vital capacity (FVC%), and modified Bhalla scores for HRCT. These parameters were evaluated and compared, at the time of chronic colonization with MRSA and MSSA, and throughout the study period.

Nutritional status was monitored through BMI obtained at the time of each evaluation at the CF center. The best annual BMI results were selected. These were used for BMI percentile calculations (for patients 2-19 years old) through the tool available at <http://www.cdc.gov/healthyweight/assessing/bmi>.<sup>18</sup>

Lung function data were evaluated through retrospective analysis on spirometric reports. The spirometric examinations were performed using the Collins Survey II computerized system (Warren E. Collins Inc., Massachusetts, USA), on patients over the age of six years who had the cognitive ability to undergo the test. The absolute values were converted to percentages of predicted values, using reference equations from Knudson et al.<sup>19</sup> The highest FEV<sub>1</sub>% and FVC% values reported for each patient every year were analyzed.

In this CF center, HRCT examinations were performed every two to four years when patients were clinically stable. These images were obtained using the ProSpeed-S™ device (General Electric, Milwaukee, WI, USA), with 1 mm slices every 10 mm, at 80 to 100 mAs (milliampere/second) and 120 kV (kilovolt), in windows of -1500 HU and at a level of 700 HU, without sedation, and with inspiration and expiration series. HRCT images were retrospectively analyzed by a pediatric radiologist and by a pulmonologist with more than 10 years of experience of CF, who had no information about any patient data. After meeting and discussing the classification adopted for the modified Bhalla score, both professionals applied it to each exam in a completely random order. The modified Bhalla score had been previously validated at another study at this institution.<sup>11</sup> The total score is obtained from the sum of the values for the severity and/or extent of each morphological abnormality and can range from 0 (no abnormality) to 37 (severe abnormalities in all items).<sup>10</sup>

## Statistical analysis

Descriptive statistical analyses were performed through construction of tables and graphs and through summary measurements appropriate for each variable.

In order to study the trends of several variables over time, the annual rate of change was calculated by means of simple linear

regression for each patient. The Wilcoxon nonparametric test was used to determine the statistical significance of differences between the MRSA and MSSA groups and between two moments. The Statistical Package for the Social Sciences (SPSS 17.0 for Windows) was used.

## RESULTS

Out of 170 CF patients who were followed up at this CF center, 20 (11.76%) fulfilled the criteria for chronic MRSA colonization. The comparison group was selected from among 70 CF patients who presented chronic colonization with MSSA. Twenty pairs of patients were included: 40% were female (8 pairs); 95% had pancreatic insufficiency (19 pairs); and 25% had *P. aeruginosa* coinfection (5 pairs).

The mean age at the time when cystic fibrosis was diagnosed was 2.5 years in the MRSA group and 2.1 years in the MSSA group. Seven patients were diagnosed through newborn screening test and the others through clinical features compatible with cystic fibrosis, with confirmation using sweat test. The mean follow-up time at the CF center was similar in the two groups (6.7 years for MRSA versus 7 years for MSSA). Other sociodemographic data are available as supplementary material (Annex).

In relation to nutritional status, the mean BMI values at the time of chronic colonization were similar: 15.5 (standard deviation,  $SD \pm 2.2$ ) in the MRSA group and 15.6 ( $SD \pm 3.6$ ) in the MSSA group, without significant statistical difference (P-value 0.823). The same trend was found for the mean BMI annual rate of change: 0.22 ( $SD \pm 0.49$ ) in the MRSA group and 0.19 ( $SD \pm 0.44$ ) in the MSSA group (P-value 0.852). Correspondingly, there was no statistically significant difference in BMI percentile between the time of chronic colonization (39.6 ( $SD \pm 32.3$ ) in MRSA; 39.8 in MSSA ( $SD \pm 33.1$ ); P-value 0.823) and thereafter: the mean annual rate of change in BMI percentile was 2 ( $SD \pm 8$ ) in MRSA and 1.1 ( $SD \pm 6$ ) in MSSA (P-value 0.852).

Spirometric data were available for 10 pairs of patients (who were older than six years of age). The mean values for FEV<sub>1</sub>% and FVC% were lower in the MRSA group at the time of chronic colonization. After chronic colonization, the mean annual rate of

decline in FEV<sub>1</sub>% for the MRSA group was 3.2% ( $SD \pm 1.8$ ), while in MSSA it was 2.3% ( $SD \pm 1.8$ ), but there was no statistically significant difference between the groups (P-value 0.374). Meanwhile, the mean annual rate of decline in FVC% was also higher for the MRSA group (3.2% per year,  $SD \pm 1.9$ ) than for the MSSA group (1.8% per year ( $SD \pm 1.7$ ), with a statistically significant difference (P-value 0.038) (Table 1).

The modified Bhalla score results from HRCT at the time of chronic colonization are described in Table 2. Evaluation of each pair at the time of chronic colonization showed that the Bhalla scores were higher in 16 patients with MRSA. At this time, the mean Bhalla score in the MRSA group was twice the score in the MSSA group (6.5 and 3.3, respectively), with a statistically significant difference (P-value 0.002) (Table 2). The annual rate of change of the Bhalla score was higher in 19 patients with MRSA, thus showing that there was faster progression of lung injury in the MRSA group. The mean annual rate of change in Bhalla score was four times higher in the MRSA group (1.7 points per year in MRSA and 0.4 points per year in MSSA), with a statistically significant difference (P-value < 0.001) (Table 2).

Regarding the scores for each Bhalla parameter at the time of chronic colonization, only the findings of bronchiectasis and mucous plugging were more severe in the MRSA group. There were no statistically significant differences between the groups for the other parameters (Table 3). However, the HRCT performed after chronic colonization (mean time elapsed of 4.5 years) showed that all the Bhalla scores were significantly worse in the MRSA group (Table 4). At this time, all the MRSA patients presented air trapping, mosaic attenuation/perfusion pattern, bronchial wall thickening and mucous plugging. Bronchiectasis was found in 90% of the MRSA patients.

## DISCUSSION

In the present study, careful pairing was done, considering age, gender and chronic colonization with *P. aeruginosa*, in order to eliminate confounding factors and effectively measure the impact of MRSA colonization in cystic fibrosis. It is known that there is a female survival disadvantage in CF cases<sup>20</sup> and that chronic *P. aeruginosa* infection results in a prolonged inflammatory response. The

**Table 1.** Spirometric data from patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA): at the time of chronic colonization and mean annual rate of change after chronic colonization (n = 10 pairs)

	FEV <sub>1</sub> % at the time of chronic colonization		Mean annual rate of change in FEV <sub>1</sub> % after chronic colonization		FVC% at the time of chronic colonization		Mean annual rate of change in FVC% after chronic colonization	
	MRSA	MSSA	MRSA	MSSA	MRSA	MSSA	MRSA	MSSA
Mean	68.6	91.1	-3.2	-2.3	81.6	95.4	-3.2	-1.8
Standard deviation	22.7	11.6	1.8	1.8	20.4	14.0	1.9	1.7
P-value (Wilcoxon test)	0.005		0.374		0.047		0.038	

FEV<sub>1</sub>% = predicted percentage forced expiratory volume in first second; FVC% = predicted percentage forced vital capacity.

latter is believed to cause respiratory tissue injury, which leads to progressive loss of lung function and adversely affects survival.<sup>21</sup>

Despite increasing prevalence of and morbidity associated with MRSA colonization in CF patients worldwide, little is known so far about its effects on lung damage. It is not clear whether MRSA colonization is simply a marker of greater severity of lung disease<sup>5</sup> or is an independent contributor towards lung function decline.<sup>15</sup> In our study, the lung function data (FEV<sub>1</sub>% and FVC%) were worse at the time of chronic MRSA colonization. From then on, the annual decline in FEV<sub>1</sub>% was 39% higher in the MRSA group. These findings showed a trend towards worse outcomes, although without statistical significance, probably due to the sample size. They highlight the impact of chronic MRSA colonization on airflow obstruction in CF patients, compared with those who only had MSSA. These results are consistent with those from other studies in which MRSA was shown to have a negative impact on lung function.<sup>15,22</sup> In a 10-year longitudinal cohort study that included 17,357 patients in the United States, it was reported that the decline in lung function was faster among patients with chronic MRSA colonization, after adjustment for

**Table 2.** Bhalla score among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA): at the time of chronic colonization and mean annual rate of change after chronic colonization (n = 20 pairs)

Pair	Bhalla score at time of chronic colonization		Annual rate of change in Bhalla score	
	MRSA	MSSA	MRSA	MSSA
1	14	4	1.4	0.3
2	4	2	0.8	0.1
3	8	10	3.0	0.0
4	5	5	0.6	0.2
5	4	6	2.4	-0.6
6	9	8	0.4	0.5
7	3	1	2.8	0.7
8	10	4	1.2	0.7
9	8	1	1.7	0.0
10	4	3	1.8	0.2
11	7	6	2.0	0.6
12	3	0	2.0	1.1
13	4	0	0.8	0.2
14	4	2	0.8	0.3
15	5	6	1.8	0.6
16	4	0	2.4	1.0
17	4	0	2.5	0.4
18	4	0	1.9	0.5
19	14	4	1.1	0.5
20	12	3	2.4	0.6
Mean	6.5	3.3	1.7	0.4
Standard deviation	3.6	2.9	0.8	0.4
P-value (Wilcoxon test)	0.002		< 0.001	

possible confounding variables. In that cohort, the decline in predicted FEV<sub>1</sub> of 2.06%/year was 43% more rapid than the 1.44% predicted/year among those without MRSA (P-value < 0.001).<sup>15</sup> Ren et al., using a large database of CF patients, showed that out of 1834 patients presenting *S. aureus* in respiratory tract cultures, those who were less than 18 years of age and had MRSA showed significantly greater airflow obstruction (FEV<sub>1</sub>), compared with

**Table 3.** Number of patients with each score for the different parameters at the time of chronic colonization in the methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) groups (n = 20 pairs)

Parameter	MRSA group	MSSA group score					P-value*
	score	Total	0	1	2	3	
Severity of bronchiectasis	0	10	10	0	0	0	0.063
	1	8	3	5	0	0	
	2	2	2	0	0	0	
	3	0	0	0	0	0	
	Total	20	15	5	0	0	
Peribronchial thickening	0	2	1	1	0	0	0.092
	1	16	6	9	1	0	
	2	2	1	1	0	0	
	3	0	0	0	0	0	
	Total	20	8	11	1	0	
Extent of bronchiectasis	0	10	10	0	0	0	0.031
	1	5	1	4	0	0	
	2	4	3	1	0	0	
	3	1	1	0	0	0	
	Total	20	15	5	0	0	
Extent of mucous plugging	0	10	9	1	0	0	0.035
	1	7	5	2	0	0	
	2	3	1	2	0	0	
	3	0	0	0	0	0	
	Total	20	15	5	0	0	
Generation of bronchial divisions	0	10	10	0	0	0	0.063
	1	6	2	4	0	0	
	2	3	2	0	1	0	
	3	1	1	0	0	0	
	Total	20	15	4	1	0	
Collapse/consolidation	0	8	5	0	3	0.212	
	1	9	9	0	0		
	2	3	2	1	0		
	Total	20	16	1	3		
	Mosaic perfusion	0	4	2	2		0
1		14	7	6	1		
2		2	0	2	0		
Total		20	9	10	1		
Air trapping		0	0	2	2	0	0.146
	1	14	7	6	1		
	2	2	0	2	0		
	Total	20	9	10	1		

\*P-value obtained via Wilcoxon test.

Note: The items "sacculations/abscesses"; "emphysema"; "acinar nodule"; "thickening of intralobular septa" and "ground glass" were not analyzed individually because almost all scores were zero.

MSSA patients.<sup>22</sup> However, their study did not match patients according to age and gender, which are significant confounders and could have influenced the outcome. Despite the knowledge that the rate of transient infection with MRSA can reach up to 69%,<sup>15</sup> patients with only one positive culture could still be included in the MRSA group in their study.<sup>22</sup> Our study provides

consistent data, in that it only included patients with chronic MRSA colonization, so as to provide better understanding of the lung function repercussions of this bacterium.

Lung function data (especially FEV<sub>1</sub>%) and the respiratory exacerbation rate have been widely used as sensitive markers. However, since advances in CF treatment have been able to delay the loss of lung function, other measurements have been revealed to be important for monitoring CF patients, including nutritional indices such as BMI.<sup>6</sup> The association of better nutritional status with improved lung function is well documented, and poor nutrition is a risk factor for accelerated decline in lung function. Data from 6,835 CF patients in the German CF Registry (1995-2005) found that low BMI (< 19 kg/m<sup>2</sup>) and low FEV<sub>1</sub> (< 80%) correlated with mortality.<sup>6</sup> Identifying risk factors that may contribute to the rate of decline of lung function and BMI may help in focusing interventions.<sup>6</sup> Few studies have discussed the effects of MRSA colonization on nutritional status. A retrospective study (2003-2007) identified 12 pediatric patients presenting MRSA colonization. After one year of MRSA colonization, only one patient showed a decrease in BMI percentile.<sup>23</sup> In our study, there were no significant differences between the groups regarding BMI or BMI percentile at the time of chronic MRSA colonization, or in the annual rate of decline of BMI.

With the recent advances in therapeutic approaches towards CF, it is essential to identify tools that can monitor lung disease progression and response to treatment.<sup>7</sup> Imaging examinations are able to detect early disease progression, thereby contributing to treatment effectiveness and quality of life among CF patients. Furthermore, HRCT can be used both for patients who are unable to undergo spirometry and for analysis on the two tests, since HRCT shows early changes in patients with normal spirometry.<sup>24</sup> Several studies have shown that despite stable spirometric parameters, HRCT scores show annual progression in total CT score.<sup>7</sup> Despite the well-established importance of HRCT scores for CF, few studies have made reference to these scores in different microbiological groups,<sup>11</sup> with no published data regarding MRSA colonized patients. In this context, our study highlights the importance of HRCT scores in CF patients with chronic colonization with MRSA, thus making a significant contribution towards aiding clinicians who deal with this group of patients.

The importance of certain lung morphological abnormalities is emphasized in the modified Bhalla scoring system. The parameter "mucous plugs", for example, is scored separately because of their crucial role in the pathogenesis of bronchiectasis. Likewise, peribronchial thickening reflects the presence of recurrent chronic infection that results in bronchial and peribronchial inflammation and/or fibrosis, which should be scored separately. These two abnormalities are of great importance in managing CF, since they might suggest

**Table 4.** Number of patients with each score for the different parameters after\* chronic colonization in the methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) groups (n = 20 pairs)

Parameter	MRSA group score	MSSA group score					P-value**
		Total	0	1	2	3	
Severity of bronchiectasis	0	2	2	0	0	0	< 0.001
	1	8	5	2	1	0	
	2	3	2	0	1	0	
	3	7	2	4	1	0	
	<b>Total</b>	<b>20</b>	<b>11</b>	<b>6</b>	<b>3</b>	<b>0</b>	
Peribronchial thickening	0	0	0	0	0	0	0.004
	1	8	0	7	1	0	
	2	9	1	7	1	0	
	3	3	0	3	0	0	
	<b>Total</b>	<b>20</b>	<b>1</b>	<b>17</b>	<b>2</b>	<b>0</b>	
Extent of bronchiectasis	0	2	2	0	0	0	0.001
	1	7	5	1	1	0	
	2	4	1	0	3	0	
	3	7	3	3	1	0	
	<b>Total</b>	<b>20</b>	<b>11</b>	<b>4</b>	<b>5</b>	<b>0</b>	
Extent of mucous plugging	0	0	0	0	0	0	0.001
	1	12	6	5	1	0	
	2	4	4	0	0	0	
	3	4	1	2	1	0	
	<b>Total</b>	<b>20</b>	<b>11</b>	<b>7</b>	<b>2</b>	<b>0</b>	
Generation of bronchial divisions	0	3	3	0	0	0	< 0.001
	1	4	2	2	0	0	
	2	5	4	0	1	0	
	3	8	3	3	2	0	
	<b>Total</b>	<b>20</b>	<b>12</b>	<b>5</b>	<b>3</b>	<b>0</b>	
Collapse/consolidation	0	4	4	0	0	0	< 0.001
	1	12	10	2	0	0	
	2	4	2	2	0	0	
	<b>Total</b>	<b>20</b>	<b>16</b>	<b>4</b>	<b>0</b>	<b>0</b>	
	Mosaic perfusion	0	0	0	0	0	
1		10	3	7	0	0	
2		10	3	6	1	0	
<b>Total</b>		<b>20</b>	<b>6</b>	<b>13</b>	<b>1</b>	<b>0</b>	
Air trapping		0	0	0	0	0	0
	1	10	3	7	0	0	
	2	10	3	6	1	0	
	<b>Total</b>	<b>20</b>	<b>6</b>	<b>13</b>	<b>1</b>	<b>0</b>	

\*Mean time elapsed of 4.5 years; \*\*P-value obtained via Wilcoxon test.

Note: The items "sacculations/abscesses"; "emphysema"; "acinar nodule"; "thickening of intralobular septa" and "ground glass" were not analyzed individually because almost all scores were zero.

the need for a specific therapeutic approach.<sup>9</sup> Simultaneously, presence of bronchiectasis in CF cases has been correlated with chronic bronchial disease, consequent to persistent inflammation and subsequent weakening of the airway wall, thereby resulting in irreversible distension of the bronchial walls.<sup>25</sup>

The importance of these considerations stood out in the present study, from which it was evident that abnormalities such as bronchiectasis, peribronchial thickening and mucous plug formation were present in almost all patients with chronic MRSA colonization. These results are concordant with analyses from other studies in which the three most prevalent abnormalities were bronchiectasis (86-90%), peribronchial thickening (53-80%) and mucous plugging (63-79%).<sup>11,26-28</sup>

In the present study, the modified Bhalla score values demonstrated that MRSA patients showed greater structural lung damage at the time of chronic colonization. At that time, detailed analysis on each parameter of the Bhalla score showed that for two of them, there were statistically significant differences between the groups (extent of bronchiectasis and mucous plugging). After chronic MRSA colonization, there was marked progression of structural lung damage, as demonstrated through the total modified Bhalla score and all its parameters individually. The presence of bronchiectasis in all patients with chronic MRSA colonization highlights the severity of injuries in this group and confirms the association of MRSA colonization with progression of structural lung injury in CF patients.

Although the other more prevalent injuries, such as peribronchial thickening, mucous plugging and mosaic perfusion, are known to be reversible, these were also more frequent in the MRSA group. This evidence supports the hypothesis that chronic MRSA colonization leads to a more prominent inflammatory response and earlier structural lesions. The mechanisms proposed for this effect may be similar to those proposed for MRSA pneumonia in non-CF patients. It is possible that MRSA remains in the respiratory tract for longer times because of its resistance to commonly used antibiotics. Moreover, presence of toxins and virulence factors may mediate greater degrees of airway inflammation.<sup>29,30</sup>

The present study is unprecedented in Brazil. It determined the relationship between clinical data and chronic colonization with MRSA, an emergent bacterium in CF cases for which greater understanding of the impact of chronic infection is needed. However, the present study has limitations because of its retrospective nature and small sample size, especially in relation to lung function tests, and these may have interfered with the statistical significance of the results. Despite these limitations, the implications of our findings strengthen the argument for development of possible evidence-based MRSA eradication measures and serve as a starting point for future studies on CF patients with chronic MRSA colonization.

## CONCLUSION

These MRSA-colonized CF patients presented greater degrees of functional and structural lung disease at the time of chronic colonization, and disease progression seemed to be faster. This was shown through comparisons in which potential confounding variables were controlled for.

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**Annex.** Pairing between patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) according to gender, age, time of chronic colonization with *S. aureus* and chronic coinfection with *P. aeruginosa*

Pair		Gender	Birth date	Chronic colonization with <i>S. aureus</i>	Colonization with <i>P. aeruginosa</i>
1	MRSA	F	May 21, 2007	2009	No
	MSSA	F	Dec 17, 2007	2009	No
2	MRSA	F	Jul 11, 2003	2009	No
	MSSA	F	Nov 3, 2003	2010	No
3	MRSA	F	Sep 4, 2009	2012	No
	MSSA	F	Mar 9, 2008	2011	No
4	MRSA	M	Oct 27, 1997	2007	No
	MSSA	M	Dec 10, 1996	2008	No
5	MRSA	M	May 24, 2011	2012	No
	MSSA	M	Jul 20, 2011	2012	No
6	MRSA	F	Jan 15, 1996	2006	Yes
	MSSA	F	Feb 18, 1998	2007	Yes
7	MRSA	M	Nov 28, 2007	2009	No
	MSSA	M	Feb 15, 2007	2009	No
8	MRSA	F	Oct 7, 1998	2010	Yes
	MSSA	F	Jul 31, 1998	2007	Yes
9	MRSA	M	Jul 13, 2006	2011	No
	MSSA	M	Jul 2, 2006	2012	No
10	MRSA	M	Sep 23, 2006	2011	No
	MSSA	M	Jun 28, 2006	2010	No
11	MRSA	M	Aug 29, 1995	2008	No
	MSSA	M	Nov 6, 1997	2010	No
12	MRSA	F	Nov 30, 2006	2008	No
	MSSA	F	Sep 15, 2008	2010	No
13	MRSA	M	Aug 20, 1995	2009	No
	MSSA	M	Aug 1, 1996	2009	No
14	MRSA	M	Apr 2, 2008	2009	No
	MSSA	M	Feb 20, 2009	2010	No
15	MRSA	M	May 12, 2000	2010	Yes
	MSSA	M	Nov 28, 2000	2008	Yes
16	MRSA	M	Jan 11, 2006	2007	No
	MSSA	M	Jul 7, 2004	2007	No
17	MRSA	M	Feb 27, 2009	2010	No
	MSSA	M	Feb 9, 2009	2010	No
18	MRSA	F	Dec 3, 2011	2012	No
	MSSA	F	Jul 14, 2011	2012	No
19	MRSA	F	Dec 28, 2001	2008	Yes
	MSSA	F	Jun 1, 2000	2007	Yes
20	MRSA	M	Sep 1, 1996	2011	Yes
	MSSA	M	Nov 10, 1996	2007	Yes

# Accuracy of spirometry for detection of asthma: a cross-sectional study

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## KEY WORDS:

Asthma.  
Spirometry.  
Methacholine chloride.  
Dimensional measurement accuracy.  
Diagnosis.  
Bronchial hyperreactivity.

## ABSTRACT

**BACKGROUND:** Asthma is a chronic inflammatory disease with airway hyperresponsiveness. Spirometry is the most commonly used test among asthmatic patients. Another functional test used for diagnosing asthma is the bronchial challenge test. The aim of this study was to analyze the accuracy of spirometry for detecting asthma in the general population.

**DESIGN AND SETTING:** Cross-sectional study with data analysis to evaluate the accuracy of spirometry through calculating sensitivity, specificity and predictive values and through the kappa agreement test.

**METHODS:** Subjects who constituted a birth cohort were enrolled at the age of 23 to 25 years. Spirometric abnormality was defined as reduced forced expiratory volume in one second, i.e. lower than 80% of the predicted value. Measurement of bronchial responsiveness was performed by means of the bronchial challenge test with methacholine. The gold-standard diagnosis of asthma was defined as the presence of bronchial hyperresponsiveness in association with respiratory symptoms.

**RESULTS:** Asthma was detected in 200 subjects (10.4%) out of the sample of 1922 individuals. Spirometric abnormality was detected in 208 subjects (10.9%) of the sample. The specificity of spirometric abnormality for detecting asthma was 90%, sensitivity was 23%, positive predictive value was 22%, and negative predictive value was 91%. The kappa test revealed weak agreement of 0.13 (95% confidence interval, CI: 0.07-0.19) between spirometry and the diagnosis of asthma.

**CONCLUSION:** Spirometry, as a single test, has limitations for detecting asthma in the general population.

## INTRODUCTION

Asthma is a chronic inflammatory disease of the airways in which many cells and mediators have a role. Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early in the morning.<sup>1</sup> The medical history and a physical examination are frequently sufficient for diagnosing asthma. In epidemiological studies and for screening for asthma in large groups (for example, employees at risk, students and the military), a diagnosis of asthma may be made based on questionnaires, with or without a physiological test.<sup>2</sup>

Spirometry is the most commonly used test for asthmatic patients. It is useful for making the diagnosis, classifying the severity and monitoring therapeutic drug administration.<sup>3</sup> Use of spirometry is valued in most guidelines on approaches to and treatment of asthma.<sup>3,4</sup>

Another functional test that is used for diagnosing asthma is measurement of airway responsiveness, i.e. the bronchial challenge test.<sup>5</sup> This test uses bronchoconstriction stimuli, such as methacholine, and it is considered to be the best choice for diagnosing asthma in patients with normal spirometry tests.<sup>5,6</sup>

Bronchial challenge corroborates the diagnosis of asthma through confirming the presence of bronchial hyperresponsiveness. More importantly, it may rule out this diagnosis when bronchial hyperresponsiveness is not detected, because its negative predictive value is high.<sup>2</sup> For this reason, it is considered to be a gold standard test for asthma diagnosis.

Untreated asthma results in significant morbidity. It carries high costs, due not only to health expenditure but also to loss of productivity, absence from school or work and impairment of family life.<sup>1</sup> One example of the importance of early asthma diagnosis is the case of work-related asthma, in which the sooner asthma is detected, the better the patient's prognosis will be.<sup>1</sup>

## OBJECTIVE

The aim of this study was to analyze the accuracy of spirometry for detecting asthma in the general population, by means of calculating sensitivity and specificity and using the kappa agreement test. A positive methacholine challenge test in combination with respiratory symptoms was used as the gold-standard method for diagnosing asthma.

## METHODS

This was a cross-sectional study with data analysis to evaluate the accuracy of spirometry for detecting asthma. Spirometric abnormality was defined here as reduced forced expiratory volume in one second (FEV<sub>1</sub>), i.e. lower than 80% of the predicted value. Measurements of bronchial responsiveness were made and a gold-standard diagnosis of asthma was defined as the presence of bronchial hyperresponsiveness and respiratory symptoms.<sup>7</sup>

### Sample

Subjects who constituted a birth cohort were enrolled in this study at the age of 23 to 25 years. We randomly selected 2,063 subjects and 1,922 of them underwent all the procedures necessary for this study.

This birth cohort comprised subjects born in the municipality of Ribeirão Preto during the period from June 1, 1978, to May 31, 1979, and this data collection was the fourth study on this cohort.<sup>7</sup>

The recruitment of the sample was based on the charts of the liveborns of the original cohort, which contained the name and address of the mother and the data of birth of the child. The potential participants in this evaluation were identified by the contact and field teams, which were set up and trained over a six-month period. A period of 24 months was reserved for subject identification and for data collection, with a capacity of 4-7 daily evaluations by the service.<sup>7</sup>

The inclusion criteria were that the subjects needed to belong to this cohort and to be able to perform all the procedures necessary. Previous articles have reported on the history of this cohort, sample size calculations, subject selection and recruitment.<sup>7</sup>

This sample was assessed in the fourth phase of following up this cohort.<sup>7</sup> The aim of this fourth phase was to ascertain the importance of events that occurred between the prenatal period and early adulthood and to analyze the impact of these events on the growth and development of chronic non-transmissible adult diseases, such as asthma. At this phase, anthropometric measurements were taken, blood samples were collected and spirometry, skin allergy tests and the bronchial challenge test with methacholine were performed. Asthma was one of the diseases studied. The methacholine challenge was performed on the whole sample to evaluate asthma for the several analyses on this cohort. Some of these analyses have already been published.<sup>7-10</sup>

The tests and measurements were carried out in a healthcare setting with easy access to medical facilities. The examinations were performed at the university hospital in the city of Ribeirão Preto, in the northwestern region of the state of São Paulo, Brazil. The participants signed a consent form after reading and listening to the aims and procedures included in the study. This study was approved by the institutional ethics committee.

## Procedures

### *Respiratory and occupational questionnaires*

Respiratory symptoms were assessed using the European Community Respiratory Health Survey (ECRHS) questionnaire, as translated into Portuguese and adapted to the Brazilian lexicon.<sup>8</sup> The ECRHS questionnaire was developed for use among young adults aged 20 to 44 years, to explore asthma symptoms in young adults. We used questions of the ECRHS questionnaire to explore asthma symptoms. Subjects could answer yes or no to the following questions:

- “Have you had wheezing or whistling in your chest at any time in the last 12 months?”
- “Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?”
- “Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?”
- “Have you been woken by an attack of shortness of breath at any time in the last 12 months?”

Presence of any of these symptoms in association with bronchial hyperresponsiveness defined asthma. Thus, symptoms reported by non-hyperresponsive individuals were not enough to classify them as asthmatic.

### **Spirometry and bronchial responsiveness measurements**

The bronchial responsiveness to methacholine was measured using the two-minute tidal breathing method. Increasing concentrations of methacholine (0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/ml) were aerosolized using a DeVilbiss 646 nebulizer (Sunrise Medical HHG Inc, Somerset, PA, USA) driven by a computer-activated dosimeter (Koko Digidoser System, PDS Instrumentation, Inc., Louisville, CO, USA) with an output of 9 ml per 0.6 second (total delivery of 0.045 ml).

FEV<sub>1</sub> was measured at baseline and 2 minutes after each tidal breathing period. The test was stopped when either a 20% fall in FEV<sub>1</sub> was achieved or the final concentration was reached. The challenge concentration causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) was calculated using the Koko software. We considered PC<sub>20</sub> ≤ 4 mg/ml to indicate bronchial hyperresponsiveness. The contraindications for the methacholine

challenge test were all conditions that might compromise the quality of the test or that might subject the patient to increased risk or discomfort, and these included FEV1 < 50% of predicted value, pregnancy, nursing mothers and inability to perform spirometry of acceptable quality. Other contraindications were heart attack or stroke in the last three months; uncontrolled hypertension; systolic blood pressure (BP) > 200 mmHg or diastolic BP > 100 mmHg; known aortic aneurysm; and current use of cholinesterase inhibitor medication (for myasthenia gravis). During preparation, patients were questioned about factors that could increase or decrease bronchial responsiveness, such as current respiratory infection.<sup>2</sup>

The hypothesis of the study was formulated after data collection. To avoid bias, the same investigator performed all tests on every volunteer. The main measurements, as described above, were symptom evaluation, FEV1 and bronchial responsiveness measurements. Based on these data, the variables were defined as follows.

### Variables

**Current wheezing** was defined as a positive answer to the question: "Have you had wheezing or whistling in your chest any time in the last 12 months?" Possible answers: yes or no.

**Chest tightness** was defined as a positive answer to the question: "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?" Possible answers: yes or no.

**Breathlessness** was defined as a positive answer to the question: "Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?" Possible answers: yes or no.

**Nocturnal breathlessness** was defined as a positive answer to the question: "Have you been woken by an attack of shortness of breath at any time in the last 12 months?" Possible answers: yes or no.

**Reduced FEV1** was defined as any value less than 80% of the predicted FEV1. Reference values were adopted as described by Crapo et al.<sup>11</sup> Thus, this quantitative variable was handled as a binary variable (FEV1 reduction: yes or no).

**Presence of asthma**, as confirmed through the bronchial hyperresponsiveness test, was defined by two main components of the disease, i.e. presence of bronchial hyperresponsiveness and at least one of the symptoms.<sup>2,5</sup> Thus, bronchial hyperresponsiveness was handled as a binary variable (positive or negative) to define asthma.

### Sample size

The sample size was defined from previous prevalence studies in which the data gathered formed the database that allowed us to conduct the present analysis.

### Statistical analysis

Simple exploratory analyses were used to describe the study population and to calculate the prevalence of reduced FEV1,

hyperresponsiveness, respiratory symptoms and asthma, expressed as percentages.

We first tested the association between reduced FEV1 (under test here) and asthma as confirmed through the methacholine challenge test (gold standard). If there was no association, we would not pursue this to test its accuracy.

The simple and multiple log-binomial regression method was used to estimate the prevalence ratio, since the response was binary (presence of disease = yes or no). In assessing the association between reduced FEV1 and asthma, the confounding variables were schooling, type of work, smoking, physical activity, blood pressure, allergy and anthropometry.

The presence of bronchial hyperresponsiveness (i.e. a positive result from the methacholine challenge) in subjects with symptoms was the definition used for asthma (gold standard). The accuracy of FEV1 reduction for detecting asthma was tested through calculation of positive and negative likelihood ratios and sensitivity and specificity. The kappa test was applied to check for agreement between reduced FEV1 and asthma. The analyses were carried out using STATA version 9.1 (Copyright 1984-2005; Stata Corp., 4905 Lakeway Drive, College Station, Texas 77845, USA).

### RESULTS

The age of the sample of 1922 individuals (980 women) who completed the protocol (mean  $\pm$  standard deviation, SD) was 23.9  $\pm$  0.7 years. The prevalence of asthma was 10.4% and 119 subjects (6.1%) were using asthma medications. The prevalences of the major variables are shown in Table 1. Bronchial hyperresponsiveness was detected in 22.2% of the sample, i.e. 427 subjects: 263 women (61.6%) and 164 men (38.4%) ( $P < 0.0001$ ). Current smoking was reported by 17.4% of the individuals, i.e. by 14.2% of the women and 20.7% of the men ( $P < 0.0001$ ). The prevalence of current plus former smoking was 26.3%, i.e. 21.9% of the women and 30.8% of the men ( $P < 0.0001$ ). Slightly

**Table 1.** Prevalence of reduced FEV1, hyperresponsiveness, respiratory symptoms and asthma

Variables	Total		Males (n = 942)		Females (n = 980)	
	n	%	n	%	n	%
Wheezing	366	19.05	159	16.90	207	21.12
Chest tightness	231	12.04	65	6.91	166	16.96
Shortness of breath at rest	229	11.92	61	6.48	168	17.14
Breathlessness	169	8.80	49	5.21	120	12.24
PC20 $\leq$ 4 mg/ml	427	22.22	164	17.41	263	26.84
Reduced FEV1	208	10.88	88	9.41	120	12.30
Asthma	200	10.40	67	7.10	133	13.60

FEV1 = forced expiratory volume in one second; Reduced FEV1 means values below 80% of predicted value; PC20 = challenge concentration causing 20% decrease in FEV1; PC20  $\leq$  4 mg/ml = bronchial hyperresponsiveness.

more than one third of the individuals belonged to the categories of qualified and semi-qualified manual workers; 21.5% to the unqualified manual category; 21.1% to the non-manual category; and 22.7% did not belong to the economically active population. Regarding educational background, 14.7% had had 1-8 years of schooling, 50.9% had had 9-11 years and 34.4% had had more than 11 years.

In the 208 cases with FEV1 reduction, the FEV1/FVC ratio (% of predicted value) was  $82 \pm 6\%$  (mean  $\pm$  SD). Since 90% of the predicted value is considered to be the cutoff value for this variable, these findings indicate that there was a reduction in FEV1/FVC in the group with FEV1 reduction. The prevalence of FEV1/FVC reduction in this group was 70%. FEV1 (% of predicted value) for the group with reduced FEV1 (n = 208) was  $73 \pm 0.06\%$ .

The association between asthma and reduced FEV1 is shown in Table 2. The kappa index calculated to assess the agreement between reduced FEV1 and asthma was 0.13 (range, 0.07 - 0.19), thus indicating weak agreement. The sensitivity, specificity, predictive values, positive likelihood ratio and negative likelihood ratio for reduced FEV1 to detect asthma were 23%, 90%, 22%, 91%, 2.30 and 0.86, respectively (Table 3). The prevalences of reduced FEV1 in cases of confirmed asthma and in cases of non-asthma are shown in Table 4.

## DISCUSSION

The aim of this study was to analyze the accuracy of spirometry for detection of asthma in general or specific populations. Accuracy was evaluated by means of calculation of sensitivity and specificity and use of the kappa agreement test. A positive methacholine challenge test in combination with asthma symptoms was used

**Table 2.** Univariate and multivariate binomial analysis on reduced FEV1

	Univariate analysis	Multivariate analysis
	PR (95% CI)	PR (95% CI)
Asthmatic	2.45 (1.83-3.29)	2.08 (1.52-2.84)
Level of schooling 1	0.70 (0.34-1.42)	0.82 (0.39-1.75)
Level of schooling 2	0.62 (0.32-1.19)	0.79 (0.39-1.61)
Level of schooling 3	0.41 (0.21-0.81)	0.70 (0.33-1.49)
Skilled crafts	1.20 (0.70-2.03)	1.22 (0.69-2.15)
Semi-skilled manual work	2.13 (1.34-3.36)	1.87 (1.12-3.12)
Unskilled manual work	2.01 (1.33-3.03)	1.75 (1.09-2.80)
Smoking	1.09 (0.78-1.51)	1.07 (0.76-1.49)
Regular physical activity	1.45 (1.12-1.88)	1.30 (1.00-1.69)
Waist-to-height ratio	1.04 (0.79-1.37)	1.07 (0.81-1.42)
Arterial blood pressure	0.71 (0.50-1.00)	0.76 (0.53-1.09)
Allergy	1.09 (0.84-1.42)	1.05 (0.80-1.38)

FEV1 = forced expiratory volume in one second; PR = prevalence ratio; CI = confidence interval; level of schooling 1 = 9-11 years of schooling; level 2 = 5-8 years of schooling; level 3 = 4 years of schooling or less. FEV1 reduction means values below 80% of predicted value.

as the gold-standard reference method for diagnosing asthma. A preliminary statistical analysis was conducted to investigate the association between abnormal spirometry and asthma in this sample. This first step confirmed that there was an association between reduced FEV1 and asthma. However, subsequent analyses indicated that spirometry underdiagnosed asthma. The sensitivity of spirometry was 23%, specificity was 90%, negative predictive value was 91% and positive predictive value was 22%. The accuracy calculated using the Youden index was low (0.33). The agreement between asthma and reduced FEV1 was also low according to the kappa coefficient (0.13). Figure 1 shows the data relating to this lack of agreement.

**Table 3.** Sensitivity, specificity, predictive values and likelihood ratio values for reduced FEV1 to detect asthma

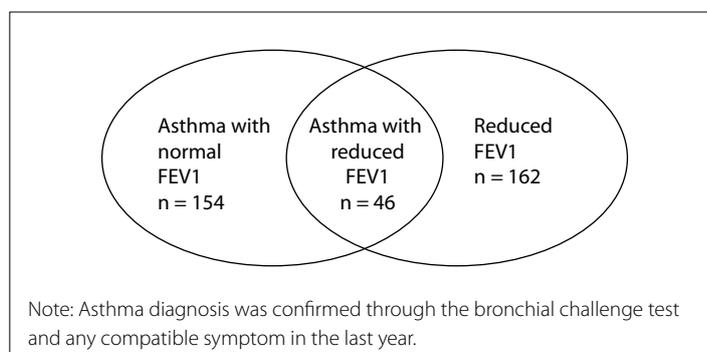
Parameter	Value
Sensitivity	23%
Specificity	90%
Positive predictive value	22%
Negative predictive value	91%
Positive likelihood ratio	2.30
Negative likelihood ratio	0.86

FEV1 = forced expiratory volume in one second; reduced FEV1 means values < 80% of predicted value. Asthma was defined as positive methacholine bronchial challenge test in association with any compatible symptom.

**Table 4.** Reduced FEV1 in cases of confirmed asthma and in cases of non-asthma

	Confirmed asthma	Non-asthma	Total
	n = 200	n = 1,722	1,922
Reduced FEV1	46	162	208
Normal FEV1	154	1,560	1,714

FEV1 = forced expiratory volume in one second; Reduced FEV1 means values below 80% of predicted value; Asthma was defined as positive methacholine bronchial challenge test in association with any compatible symptom.



Note: Asthma diagnosis was confirmed through the bronchial challenge test and any compatible symptom in the last year.

**Figure 1.** Number of subjects with asthma and with reduced forced expiratory volume in one second (FEV1).

This high negative predictive value for spirometry (91%) means that a negative test (normal spirometry) probably indicates absence of asthma. It is worthy bearing in mind that predictive value calculations are influenced by prevalence, i.e. the low probability of asthma in this case of a negative test was also a consequence of the low prevalence of asthma (10.4%). The low sensitivity of this test indicates that it is not suitable for disease screening. Although spirometry is a cheap, common and simple health screening test that, for example, can be used for workers exposed to high-risk pollutants, it is insufficient for detecting most cases of asthma.<sup>12</sup>

In the first study evaluating the diagnostic accuracy of spirometry for diagnosing airflow obstruction in patients with asthma or chronic obstructive pulmonary disease (COPD) in primary care, it was found that the presence or absence of COPD could be estimated with comparatively high diagnostic accuracy. It was also possible to accept the presence of asthma. However, it was impossible to rule out asthma because the sensitivity was too low. The sensitivity for diagnosing airway obstruction in asthma cases was 29% (95% confidence interval, CI: 21-39) and the specificity was 90% (95% CI: 81-95).<sup>13</sup> These figures were similar to our findings.

Four commonly used tests for diagnosing asthma were assessed in a population-based sample of 495 schoolchildren (the Odense Schoolchild Study). The test panel consisted of FEV<sub>1</sub>, challenge with treadmill exercise, challenge with inhaled methacholine and monitoring of peak expiratory flow (PEF), twice daily for two weeks. The agreement between the four tests was weak. The sensitivity for diagnosed asthma was highest for the methacholine challenge followed by PEF monitoring, whereas the specificity for asthma or asthma-like symptoms was marginally higher with the other two tests (spirometry and challenge with exercise).<sup>14</sup> Finally, Bonini et al. reported that spirometry appeared to be poorly sensitive for detecting mild persistent or intermittent asthma in athletes, possibly because exercise necessities are associated with spirometry values of approximately 100% of predicted values in most athletes.<sup>15</sup>

Most definitions of asthma highlight variable airflow obstruction and inflammation as essential elements of this condition. These characteristics do not translate into an unambiguous definition to separate asthma and non-asthma in surveys and in screening approaches. In previous studies from our group, we showed that non-dichotomous definitions of asthma may lead to different results regarding the prevalence of and risk factors for asthma.<sup>16</sup> Nevertheless, asthma definitions depend on the purposes of the diagnosis and definitions based on spirometry are scarcely found in epidemiological studies.<sup>16,17</sup>

Conversely, for medical practice, use of spirometry is certainly more important because patients have asthma of greater severity and present with bronchial obstruction. Measurement of FEV<sub>1</sub> is necessary for classifying its severity and for follow-up. In cases

with normal spirometry and unconfirmed asthma, bronchial challenge with methacholine is the test of choice.<sup>2</sup>

Work-related asthma is the most prevalent occupational respiratory disease. It is defined as asthma that is causally and specifically related to exposure to airborne dust, gases, vapors or fumes in the workplace. Work-related asthma encompasses aggravated asthma (meaning preexisting asthma) and occupational asthma (without preexisting asthma).<sup>2</sup> Patients' prognoses depend on the duration of exposure, duration of symptoms and severity of asthma at the time of diagnosis. Patients with asthma of greater severity tend to continue to present asthma symptoms after exposure ceases, but those with mild asthma may subsequently achieve complete remission.<sup>2</sup> Therefore, early diagnosing of asthma and exposure cessation are the most important approaches for work-related asthma.<sup>1</sup>

Brazilian regulation NR-7 requires annual spirometry for workers dealing with non-fibrogenic aerosols. Our finding that spirometry has low sensitivity for detecting asthma in the general population does not support this policy. Instead, regulations should encourage use of the bronchial challenge test and symptom questionnaires to detect asthma cases with normal spirometry. Other manifestations that precede asthma could also improve patients' odds of early detection and cure for occupational asthma. These may include occurrences of rhinitis, skin symptoms and allergic sensitization. Therefore, NR-7 may lead to detection of asthma at a later stage than would be recommendable.<sup>12</sup>

However, the purpose of the present analysis was not to examine the efficacy of the regulation NR-7. We mention it simply as an example of the value that is placed on spirometry, which deserves attention. If NR-7 were to be changed such that it would then recommend use of the bronchial challenge test or use of a symptom questionnaire, this would lead to earlier diagnosis of asthma in workers with high-risk exposure.

Bronchial hyperresponsiveness is the best test for detecting asthma, but this procedure carries risks and precautions are required. Occasional dramatic falls in FEV<sub>1</sub> may occur during testing and the risk of such events may be higher in individuals with low baseline lung function. The hazards and reactions include bronchoconstriction, hyperinflation with severe coughing, dizziness, lightheadedness or chest pain. Nurses or technicians who have asthma should not administer methacholine. It is difficult to implement this procedure because of the safety measures that are necessary and the costs of this procedure. Typically, the methacholine test is performed in a pulmonary function laboratory, a clinic or a physician's office. Prices in the United States may be estimated from a review article published by Sam Birnbaum and Timothy J. Barreiro in 2007: "The Centers for Medicare and Medicaid Services reimbursement for methacholine challenge test is approximately \$175. However, reimbursement from commercial insurers may vary dramatically."<sup>18</sup>

The positive features of the present study protocol were its large sample size, its excellent reference test for asthma and the young age of the participants, which practically excluded the bias of patients with COPD. One limitation of the study was its lack of diagnosis for all subjects with reduced FEV1. Asthmatics could be identified through the methacholine challenge, but other diseases with normal bronchial responsiveness were not evaluated. However, detection of reduced FEV1 was not common. Subjects without asthma but with reduced FEV1 may have obesity, chest wall disease, neuromuscular impairment, bronchiectasis or other respiratory diseases.

## CONCLUSION

The low sensitivity of spirometry for detecting asthma in clinical settings allows us to assume that this test conducted alone is not a good screening tool.

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# Cutoff values for appendicular skeletal muscle mass and strength in relation to fear of falling among Brazilian older adults: cross-sectional study

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## KEY WORDS:

Aging.  
Sarcopenia.  
Muscle, skeletal.  
Hand strength.  
Walking speed.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Sarcopenia is an emerging public health issue in Brazil. Because of its high prevalence and the lack of national data, the objective here was to identify cutoff points for appendicular skeletal muscle (ASM) and handgrip strength in relation to fear of falling among Brazilian older adults.

**DESIGN AND SETTING:** Cross-sectional study; in the community.

**METHODS:** Participants underwent morphological and functional evaluations; and were asked about previous falls and fear of falling. Different adjustments to ASM and handgrip strength were used. Slow walking speed was defined as < 0.8 m/s or 1.0 m/s. Gender and age groups were compared using t tests, analysis of variance (ANOVA), chi-square test or Fisher's exact test. Receiver operating characteristic curves were used to identify cutoffs for ASM and handgrip strength in relation to fear of falling.

**RESULTS:** 578 older adults participated in this study. Function levels decreased with increasing age, and body composition differed between the sexes. In relation to fear of falling, the cutoffs for ASM adjusted for body mass index (BMI) were < 0.85 for men and < 0.53 for women; the cutoffs for absolute handgrip strength and relative handgrip strength (adjusted for BMI) were 30.0 kgf and 21.7 kgf, and 1.07 and 0.66, for men and women, respectively.

**CONCLUSION:** The values presented can be used as references in clinical practice and research. We recommend use of ASM adjusted for BMI and choosing between absolute and relative handgrip strength for men and women, according to study needs.

## INTRODUCTION

Sarcopenia, defined as progressive loss of muscle mass and strength/functionality with aging, is an emerging public health issue in Brazil.<sup>1</sup> Loss of muscle mass and function may result in loss of physical capabilities (e.g. endurance, strength and muscle power), poor quality of life, unfavorable metabolic effects, falls and fear of falling, frailty and mortality among older adults. Sarcopenia is frequently associated with multiple morbid conditions, smoking habit, low body mass index (BMI), malnutrition and physical inactivity.<sup>2</sup>

Several consensuses and recommendations have been proposed by different institutions in attempts to standardize the conceptual approaches used to diagnose sarcopenia.<sup>2-5</sup> Among these, experts agree that three key factors should be addressed: body composition (muscle mass), functionality (e.g. walking speed) and muscle strength (e.g. handgrip strength).

It has been estimated that after the age of 50, muscle mass decreases consistently at a rate of approximately 1% per year, walking speed at a rate of 2.0-2.2% and handgrip strength at a rate of 1.9-5.0%, as a result of the transition process of decreasing lean body mass and increasing fat accumulation.<sup>6,7</sup> Cutoffs and reference values have also been presented in consensuses and recommendations. In addition to the international characteristics of the studies from which these values were compiled, most of these studies were conducted in developed countries and/or in countries that differ genetically, ethnically and culturally from Brazil. Moreover, even if the miscegenation of the Brazilian population has been taken into consideration, there are difficulties and limitations in making inferences from these values in relation to Brazilian older adults.

Great importance is now placed on sarcopenia, which recently culminated in determination of an International Classification of Diseases (ICD-10) code.<sup>8</sup> Furthermore, the rising prevalence

of sarcopenia among older Brazilians has now reached 17%,<sup>1</sup> yet there is a lack of national preliminary data. Therefore, in this light, the aim of this study was to identify cutoff values for appendicular skeletal muscle (ASM), and handgrip strength in relation to fear of falling among Brazilian older adults.

## OBJECTIVE

The aim of this study was primarily to identify evidence-based cutoff values for ASM and handgrip strength in relation to fear of falling; and secondarily, to ascertain the morphological and functional characteristics of Brazilian older adults according to gender and age groups.

## METHODS

### Design and ethics

This study had a cross-sectional design (frequency study) and data were collected during 2015 and 2016.

The present study was approved by the Ethics Committee of the University of Campinas, under protocol #39437514.0.0000.5404. All participants signed an informed consent statement in which they agreed to participate in the study, and this was signed before data collection.

### Subjects

Subjects were recruited from four community centers for older adults in southeastern and southern Brazil during the study period, and were invited to participate voluntarily in a convenience sample. In these centers, they undertook social and physical activities provided by physical educators. Although subjects were recruited mainly in community centers, individuals who were not participating in regular activities (e.g. neighbors, relatives and others living in the community) were also invited to participate. This ensured variability of this sample. It is important to mention that neither center was responsible for rehabilitation or for any kind of medical treatment.

The inclusion criteria were that the subjects should be: a) community-dwelling individuals; b) 60 years of age or older; and c) able to answer questions and perform functional and body composition tests. The exclusion criteria comprised situations of: a) uncontrolled cardiovascular or pulmonary disease, conditions associated with a risk of falling (i.e. Parkinson's disease or stroke), physical and cognitive impairment (according to reported chronic diseases, e.g. presence of conditions that might entail a requirement for assistance in basic activities of daily living) and items present in the functional assessment staging of Alzheimer's disease (verified onsite); b) use of a metal prosthesis and/or pacemaker (i.e. interference with the bioelectrical impedance analysis).

## Assessments

The assessments were divided into two steps: a) indirect assessments based on questionnaires; and b) direct assessments based on morphofunctional evaluations (i.e. anthropometric characteristics and physical function). Before the evaluations, all tests were explained in detail to all participants by an experienced researcher. Verbal encouragement was provided to ensure that the participants reached the best performance possible.

### Indirect assessments

#### *Chronic degenerative diseases, age, fear of falling and falls*

A questionnaire was used to obtain data regarding the presence of chronic diseases, age, fear of falling and occurrences of falls during the year prior to this investigation. The questionnaire was based on simple questions that were answered by means of binary constructs (i.e. yes or no), so as to avoid possible misunderstanding between the researchers and the subjects. First, an extensive list of the most prevalent chronic diseases (e.g. hypertension, diabetes or osteoporosis) among older adults was presented to the participants. They then stated whether they had any previous clinical diagnosis of the chronic condition (in the form of a yes/no response). These data are not shown and were used solely for exclusion purposes.

In relation to fear of falling, the following question was asked: "Are you afraid of falling?". The following question was asked about occurrences of falls: "Have you experienced a fall in the past year?". It is important to mention that only the question about occurrences of falls was retrospective: all the other questions and evaluations were in relation to the period within which the study was conducted.

### Direct assessments

#### *Anthropometric measurements*

Height was measured using a standard stadiometer and waist and hip circumferences using a measuring tape. The body composition was assessed by means of bioelectrical impedance analysis (BIA) (Tanita BC-108, Tokyo, Japan). The equipment provided the weight of the subject, and the height was inserted manually by the researcher. The analysis gave values for absolute and segmented muscle and fat mass. The Tanita BIA uses a frequency of 50 kHz to measure the quantity of intra and extracellular water in the body. This equipment has eight electrodes: four under the subjects' feet and four on their hands. The ASM values (sum of muscle mass of limbs) are useful for diagnosing sarcopenia.<sup>9</sup> In this study, we used several adjustments (i.e. according to BMI, height squared and weight), as well as the non-adjusted data, to ascertain the best approach for Brazilian older adults. Additional data concerning absolute skeletal muscle was also provided.

### Physical function

Walking speed was evaluated over a 10-meter distance that was clearly marked out on the ground. An additional initial distance of 2 m was also marked out, thus making an overall marked-out distance of 12 m in length. The participants were asked to walk the entire distance at their usual pace. The time required to complete the inner 10-m distance was assessed.<sup>10</sup> Walking speed was calculated as a continuous value.

Cutoffs of 0.8 m/s and 1.0 m/s cutoffs were applied. The value of 0.8 m/s has been suggested in other studies as representative of slow walking. However, considering the range in walking speed that is seen in such studies, and the characteristics of the sample that we studied, 1 m/s was also used.<sup>2,3</sup>

The timed up-and-go (TUG) test has been widely described. The time taken for the subject to stand up from a seated position on a chair, walk three meters ahead in a straight line, go round a cone and return to the chair and sit down is measured.<sup>11</sup>

Handgrip strength was measured using a Jamar digital dynamometer (Jamar Plus+; Sammons Preston, Rolyon, Bolingbrook, IL, USA). While seated, the subject held the dynamometer with elbow flexed at 90° without it touching his/her body. After preparation, the subject was instructed to pull the lever as much as possible. Each hand was tested once and the best value was used in the analysis. The subjects were also instructed to avoid the Valsalva maneuver or blocked breath while performing the test. Handle position two was set as standard for all subjects, as previously recommended.<sup>12</sup>

### Statistical analyses

All analyses were carried out using the SPSS software, version 21.0 (IBM Inc., Chicago, IL, USA) and the MedCalc statistical software version 17.2 (MedCalc Software, Ostend, Belgium). Values were presented descriptively, as the mean  $\pm$  standard deviation (SD) for continuous variables and frequency (%) for categorical values.

To compare the older adults' characteristics according to gender, unpaired t tests and chi-square tests were used for continuous and categorical variables, respectively. In analyses according to age, the subjects were divided into five groups (60 to 64, 65 to 69, 70 to 74, 75 to 79 and 80 plus years old). For continuous variables, analysis of variance (ANOVA) was used; when statistical differences were found, Tukey's post-hoc test was applied. For categorical variables, the chi-square test or Fisher's exact test was used.

In addition, receiver operating characteristic (ROC) curve analyses were used to ascertain cutoff values for ASM and handgrip strength in relation to fear of falling. For this, different adjustments of ASM and handgrip strength were used; the curves were then compared to investigate statistical differences among them. The ROC curve compares the true-positive rate (sensitivity) versus the false-positive rate (1 - specificity) across a range of values, regarding the ability to predict a dichotomous outcome. High sensitivity

corresponds to high negative predictive value, while high specificity corresponds to high positive predictive value. Sensitivity and specificity were used to identify the cutoff values for ASM and handgrip strength in this study.<sup>13</sup>

The area under the curve (AUC) measures test performance and describes the probability that a test will correctly identify individuals who did or did not have a condition and who were randomly selected from the cohort. Generally, the closer the AUC is to 1, the better the overall diagnostic performance of the test will be, and the closer to 0.5 that it is, the poorer the test will be.<sup>14,15</sup>

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios (positive [LR+] and negative [LR-]) for ASM and handgrip strength in relation to fear of falling were computed. Predictive values describe the probability that a person has a condition once the results of his or her tests are known. LR+ and LR- indicate what the odds are that a disease will increase or decrease when a test is positive or negative, respectively.

Fear of falling was selected as the primary outcome for this study because of its association with psychological and physical issues such as falls, loss of confidence, restriction of activities and social withdrawal, which may lead to dependence and disability.<sup>16,17</sup> Other variables were considered as outcomes, such as falls and walking speed; however, due to the small number of subjects with positive results or missing data, no further analyses were conducted. In all analyses, statistical significance was set at  $P < 0.05$ .

### RESULTS

In total, 578 older adults (122 males and 456 females) participated in this study. These individuals presented diversity of race, ethnicity and geographic area of origin, and a range of health and functional states. Their characteristics are shown descriptively in **Table 1**. The mean age was  $70.0 \pm 6.7$  years for males and  $69.4 \pm 6.6$  for females. Women had lower strength and were more overweight than men. Moreover, more women experienced a fall event during the year prior to this investigation (women 25.3% and men 14.4%) and reported fear of falling (women 65.7% and men 43.7%). Regarding physical function, women had slow walking speed than men (**Table 1**).

**Tables 2 and 3** present the study data according to gender, divided into age groups. The highest rates of fear of falling were shown by the group aged 80 years and over, for both men and women. However, the difference was statistically significant only for men. Among the men, those aged 60 to 64 years were stronger than those aged 80 and over, regarding the absolute values of handgrip strength. This difference was not seen when the data were adjusted according to BMI. The age group from 60 to 64 years also had higher levels of skeletal muscle (total and adjusted according to height squared) and total ASM. Regarding walking speed and

**Table 1.** Participants' characteristics

Variables	Older adults (n = 578)		P
	Male (n = 122)	Female (n = 456)	
Age (years)	70.5 ± 6.7	69.4 ± 6.6	0.11
Handgrip strength (kgf)	37.4 ± 8.1	24.2 ± 4.8	< 0.001
Relative handgrip strength (adjusted for body mass index)	1.4 ± 0.3	0.8 ± 0.2	< 0.001
Body mass index (kg/m <sup>2</sup> )	26.8 ± 3.5	28.3 ± 4.9	< 0.001
Fat percentage (%)	26.2 ± 6.1	41.1 ± 6.8	< 0.001
Total skeletal muscle mass (kg)	51.4 ± 6.7	36.2 ± 3.3	< 0.001
Skeletal muscle mass (adjusted for body mass index)	1.94 ± 0.2	1.31 ± 0.1	< 0.001
Skeletal muscle mass (kg/m <sup>2</sup> ) (adjusted for height squared)	18.4 ± 1.4	15.3 ± 0.8	< 0.001
Skeletal muscle mass (adjusted for weight)	0.7 ± 0.05	0.5 ± 0.06	< 0.001
Total appendicular skeletal muscle (kg)	25.2 ± 4.0	16.4 ± 1.8	< 0.001
Appendicular skeletal muscle (adjusted for body mass index)	0.95 ± 0.1	0.59 ± 0.08	< 0.001
Appendicular skeletal muscle (kg/m <sup>2</sup> ) (adjusted for height squared)	9.04 ± 1.0	6.9 ± 0.6	< 0.001
Appendicular skeletal muscle (adjusted for weight)	0.34 ± 0.03	0.25 ± 0.02	< 0.001
Falls during the year prior to study	17 (14.4)	113 (25.3)	0.01
Fear of falling	52 (43.7)	291 (65.7)	< 0.001
Waist circumference (cm)	97.5 ± 9.6	95.2 ± 11	0.03
Hip circumference (cm)	100.6 ± 6.3	103.5 ± 9.8	< 0.001
Timed Up and Go (s)	7.6 ± 2.6	8 ± 2.4	0.14
Usual walking speed (m/s)	1.3 ± 0.3	1.2 ± 0.2	0.03
Slow walking speed (using cutoff < 0.8 m/s)	6 (5.0)	17 (3.8)	0.56
Slow walking speed (using cutoff < 1.0 m/s)	18 (14.9)	62 (13.8)	0.77

Values are mean ± standard deviation or n (%).

**Table 2.** Characteristics of older men (n = 122) according to age

Variables	60~64 (n = 25)	65~69 (n = 35)	70~74 (n = 27)	75~79 (n = 24)	80+ (n = 11)	P
Falls during the year prior to study	3 (12.5)	5 (14.7)	3 (11.1)	3 (13.0)	3 (30.0)	0.69
Fear of falling	8 (32.0)	13 (38.2)	8 (30.8)	15 (65.2)	8 (72.7)	0.02
Waist circumference (cm)	99.9 ± 8.3	95.4 ± 8.1	99.6 ± 9.7	97.6 ± 11.3	93.4 ± 11.3	0.16
Hip circumference (cm)	102.3 ± 6	100.2 ± 4.6	100.8 ± 6.3	101.0 ± 7.4	96.4 ± 8.8	0.16
Handgrip strength (kgf)	40.4 ± 8.3	39.3 ± 6.5	37.7 ± 8.7	35.6 ± 6.8	28.6 ± 6.9 <sup>†</sup>	< 0.001
Relative handgrip strength (adjusted for body mass index)	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.4	1.3 ± 0.2	1.2 ± 0.2	0.13
Usual walking speed (m/s)	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.3	1.2 ± 0.3 <sup>†</sup>	1.0 ± 0.3 <sup>††</sup>	< 0.001
Slow walking speed (using cutoff < 0.8 m/s)	--	--	1 (3.7)	3 (12.5)	2 (18.2)	0.01
Slow walking speed (using cutoff < 1.0 m/s)	1 (4)	1 (2.9)	5 (18.5)	5 (20.8)	6 (54.5)	< 0.001
Timed Up and Go (s)	7 ± 1.8	6.6 ± 1.6	7.5 ± 2.10	8.8 ± 3.9 <sup>†</sup>	10 ± 2.4 <sup>††</sup>	< 0.001
Fat percentage (%)	27.5 ± 5.3	25.2 ± 5.9	26.7 ± 6.3	27.1 ± 5.3	22.3 ± 8.9	0.16
Body mass index (kg/m <sup>2</sup> )	27.8 ± 3.3	26.5 ± 3.2	27.1 ± 3.5	26.9 ± 3.8	23.4 ± 3.1 <sup>†</sup>	0.03
Total skeletal muscle mass (kg)	54.4 ± 6.8	52.4 ± 4.4	50.4 ± 6.5	50.8 ± 7.8	44.0 ± 5.7 <sup>†</sup>	0.001
Skeletal muscle mass (adjusted for body mass index)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.51
Skeletal muscle mass (kg/m <sup>2</sup> ) (adjusted for height squared)	18.9 ± 1.2	18.5 ± 1.5	18.4 ± 1.1	18.4 ± 1.5	17.1 ± 1.7 <sup>†</sup>	0.03
Skeletal muscle mass (adjusted for weight)	0.6 ± 0.05	0.7 ± 0.05	0.7 ± 0.05	0.6 ± 0.05	0.7 ± 0.08	0.22
Total appendicular skeletal muscle (kg)	26.3 ± 3.9	25.7 ± 2.8	26.6 ± 4.1	25.3 ± 5.0	21.6 ± 3.7 <sup>†</sup>	0.03
Appendicular skeletal muscle (adjusted for body mass index)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.70
Appendicular skeletal muscle (kg/m <sup>2</sup> ) (adjusted for height squared)	9.1 ± 0.8	9.1 ± 0.9	8.9 ± 0.9	9.0 ± 1.1	8.4 ± 1.2	0.34
Appendicular skeletal muscle (adjusted for weight)	0.3 ± 0.02	0.3 ± 0.02	0.3 ± 0.03	0.3 ± 0.02	0.3 ± 0.04	0.15

Values are mean ± standard deviation or n (%). Tukey's post-hoc test: †: ≠ 60~64; ††: ≠ 65~69.

the TUG tests, function also decreased as age increased; a similar trend was observed regarding BMI, but not regarding fat percentage (Table 2).

It was evident that older women had slower walking speed and TUG, and lower muscle strength than younger women, as shown by both absolute and relative handgrip strength. Fat percentage, BMI and skeletal muscle (total and adjusted according to BMI, height squared and weight) also decreased with increasing age. Regarding ASM, only the total value and the value adjusted according to height squared failed to show statistical differences (Table 3).

The ROC curves and comparisons among them are presented in Figure 1. Regarding ASM, the adjustment according to BMI showed the best AUC in relation to fear of falling. Cutoff values were identified both for men and for women. For men, as shown in Table 4, the cutoff was 0.85 (AUC = 0.81; 95% confidence interval, CI = 0.73-0.89;  $P < 0.001$ ). Table 5 shows the accuracy data for ASM for men and Table 6 for women. For women (Table 7), the cutoff was 0.53 (AUC = 0.76; 95% CI = 0.71-0.81;  $P < 0.001$ ).

Concerning handgrip strength, absolute values showed slight better AUC than did relative values among the men, while relative handgrip strength showed better AUC among the women. Therefore, we present cutoff values for both absolute and relative

values: for men, as shown in Table 8, the cutoff for absolute handgrip strength was 30.0 kgf (AUC = 0.75; 95% CI = 0.66-0.84;  $P < 0.001$ ). Table 9 shows the accuracy values for HGS for men, such as sensitivity, and Table 10 shows these values for women. The cutoff for women was 21.7 kgf (AUC = 0.56; 95% CI = 0.51-0.62;  $P = 0.02$ ), as shown in Table 11. The cutoffs for relative handgrip strength were 1.07 (AUC = 0.74; 95% CI = 0.65-0.83;  $P < 0.001$ ).

## DISCUSSION

This study presented reference values for strength, physical function tests, body composition, anthropometric measurements, falls and fear of falling according to age from a community-based cohort of older men and women aged 60 years and over. Moreover, cutoff values for ASM and handgrip strength, which are useful for ascertaining the existence of sarcopenia in older adults, were also presented in relation to fear of falling.

As extensively reported in the literature, differences according to gender concerning ASM, strength and body composition were observed, as well as decline in physical function with increasing age among older adults. The tests used in this study have clinical relevance, and reference values of this nature are scarce in the Brazilian literature, which increases the external validity of this study. Even though some of these values were similar to those

**Table 3.** Characteristics of older women (n = 455) according to age

Variables	60~64 (n = 127)	65~69 (n = 123)	70~74 (n = 102)	75~79 (n = 68)	80+ (n = 35)	P
Falls during the year prior to study	25 (20.2)	30 (25.0)	27 (27.0)	21 (31.3)	9 (26.5)	0.52
Fear of falling	75 (60.5)	73 (60.8)	69 (69.7)	49 (73.1)	24 (75)	0.06
Waist circumference (cm)	95.7 ± 10.9	94.9 ± 10.1	97.2 ± 12.1	92.7 ± 10.8	93.3 ± 10.2	0.07
Hip circumference (cm)	104.7 ± 9	102.7 ± 8.9	105.2 ± 11.7	101.7 ± 9.9	100.7 ± 7.3	0.03
Handgrip strength (kgf)	25.5 ± 5	25.1 ± 4.5	24.5 ± 4.4	21.5 ± 3.8 <sup>††</sup>	20.9 ± 4.7 <sup>††</sup>	< 0.001
Relative handgrip strength (adjusted for body mass index)	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.1 <sup>†</sup>	0.8 ± 0.2	0.01
Usual walking speed (m/s)	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.2 <sup>†</sup>	1.2 ± 0.3 <sup>††</sup>	1 ± 0.3 <sup>†††</sup>	< 0.001
Slow walking speed (using cutoff < 0.8 m/s)	--	3 (2.5)	1 (1.0)	7 (10.4)	6 (17.6)	< 0.001
Slow walking speed (using cutoff < 1.0 m/s)	8 (6.5)	11 (9.2)	13 (12.7)	15 (22.4)	15 (44.1)	< 0.001
Timed Up and Go (s)	7.0 ± 1.4	7.5 ± 1.9	8.2 ± 2.1 <sup>†</sup>	9.0 ± 2.9 <sup>††</sup>	11.0 ± 3.8 <sup>†††</sup>	< 0.001
Fat percentage (%)	42.0 ± 6.1	40.9 ± 6.5	42.6 ± 6.7	39.4 ± 6.9 <sup>†</sup>	37.3 ± 8.2 <sup>††</sup>	< 0.001
Body mass index (kg/m <sup>2</sup> )	29.2 ± 5.5	28.1 ± 4.2	29.1 ± 4.9	27.0 ± 4.3 <sup>††</sup>	25.9 ± 4.1 <sup>††</sup>	< 0.001
Total skeletal muscle mass (kg)	36.9 ± 3.2	36.5 ± 3.2	35.9 ± 3.3	35.2 ± 3.4 <sup>†</sup>	34.9 ± 3.7 <sup>†</sup>	0.001
Skeletal muscle mass (adjusted for body mass index)	1.3 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.3 ± 0.2 <sup>†</sup>	0.008
Skeletal muscle mass (kg/m <sup>2</sup> ) (adjusted for height squared)	15.4 ± 0.8	15.3 ± 0.8	15.4 ± 0.7	15.1 ± 0.6	14.9 ± 0.8 <sup>††</sup>	0.009
Skeletal muscle mass (adjusted for weight)	0.5 ± 0.05	0.5 ± 0.06	0.5 ± 0.05	0.5 ± 0.06 <sup>††</sup>	0.5 ± 0.07 <sup>†††</sup>	< 0.001
Total appendicular skeletal muscle (kg)	16.4 ± 1.7	16.6 ± 1.8	16.4 ± 1.8	16.1 ± 2.0	16.3 ± 2.1	0.62
Appendicular skeletal muscle (adjusted for body mass index)	0.5 ± 0.07	0.5 ± 0.07	0.5 ± 0.07	0.6 ± 0.08 <sup>†</sup>	0.6 ± 0.09 <sup>††</sup>	< 0.001
Appendicular skeletal muscle (kg/m <sup>2</sup> ) (adjusted for height squared)	6.8 ± 0.6	6.9 ± 0.6	7.1 ± 0.6	6.9 ± 0.6	7.0 ± 0.7	0.15
Appendicular skeletal muscle (adjusted for weight)	0.2 ± 0.02	0.2 ± 0.02	0.2 ± 0.02	0.2 ± 0.03 <sup>††</sup>	0.2 ± 0.03 <sup>†††</sup>	< 0.001

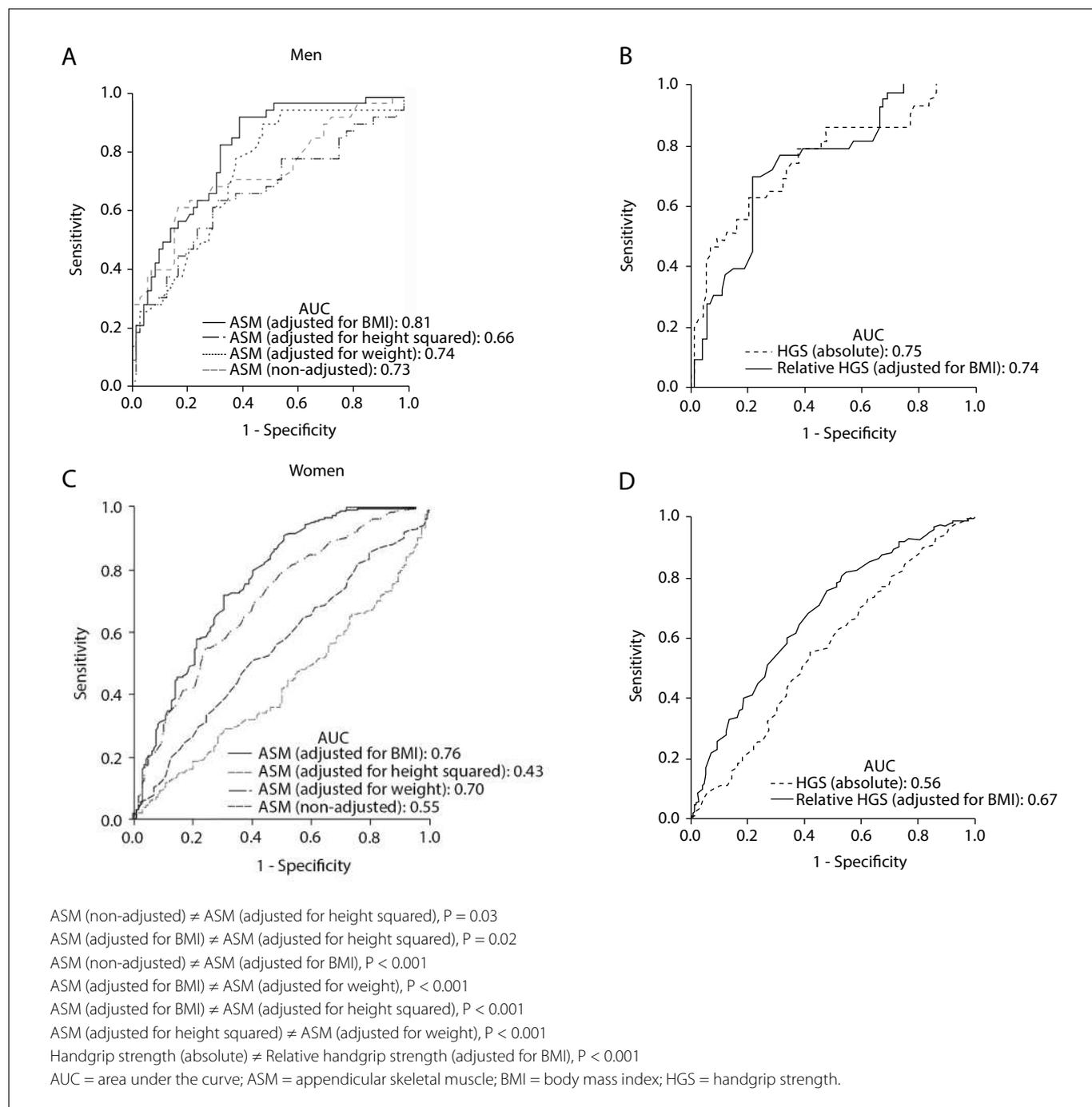
Values are mean ± standard deviation or n (%). Tukey's post-hoc test: †: ≠ 60~64; ††: ≠ 65~69; †††: ≠ 70~74; ††††: ≠ 75~79.

found in other populations, local values are preferable when available, given that regional characteristics can alter results and comparisons. These data may be useful for clinicians who need reference values to make comparisons with observed performance within clinical practice and research, and to compare different populations.

**Table 4.** Appendicular skeletal muscle (ASM) adjusted for body mass index (BMI), in relation to fear of falling among men

	Fear of falling		Total
	Present	Absent	
ASM (BMI) < 0.85	14	5	19
ASM (BMI) > 0.85	28	67	95
<b>Total</b>	<b>42</b>	<b>72</b>	<b>114</b>

Pearson chi-square  $P < 0.001$ .



**Figure 1.** Receiver operating characteristic curves for appendicular skeletal muscle with different adjustments and for handgrip strength (absolute value and adjusted for body mass index). Fear of falling was used as the outcome variable. Data on men (A-B) and women (C-D) are presented. Statistical differences among or between curves are presented, as applicable.

**Table 5.** Accuracy of appendicular skeletal muscle (ASM) for prediction of fear of falling among men

Sensitivity	{14/(14+28)}	0.33	33%
Specificity	{67/(5+67)}	0.93	93%
Positive predictive value (PPV)	{14/(14+5)}	0.73	73%
Negative predictive value (NPV)	{67/(28+67)}	0.70	70%
Positive likelihood ratio (LR+)	sensitivity/ (1-specificity)	4.71	
Negative likelihood ratio (LR-)	(1-sensitivity)/ specificity	0.72	

**Table 6.** Accuracy of relative appendicular skeletal muscle (ASM) for prediction of fear of falling among women

Sensitivity	{84/(84+194)}	0.30	30%
Specificity	{140/(12+140)}	0.92	92%
Positive predictive value (PPV)	{84/(84+12)}	0.87	87%
Negative predictive value (NPV)	{140/ (194+140)}	0.41	41%
Positive likelihood ratio (LR+)	sensitivity/ (1-specificity)	3.75	
Negative likelihood ratio (LR-)	(1-sensitivity)/ specificity	0.76	

**Table 7.** Appendicular skeletal muscle adjusted (ASM) for body mass index (BMI), in relation to fear of falling among women

	Fear of falling		Total
	Present	Absent	
ASM (BMI) < 0.53	84	12	96
ASM (BMI) > 0.53	194	140	334
<b>Total</b>	<b>278</b>	<b>152</b>	<b>430</b>

Pearson chi-square P < 0.001.

**Table 8.** Absolute\* and relative<sup>†</sup> handgrip strength (HGS) in relation to fear of falling among men

	Fear of falling		Total
	Present	Absent	
Absolute HGS < 30 kgf	18	4	22
Absolute HGS > 30 kgf	28	71	99
<b>Total</b>	<b>46</b>	<b>75</b>	<b>121</b>
Relative HGS (BMI) < 1.07	12	5	17
HGS (BMI) > 1.07	31	69	100
<b>Total</b>	<b>43</b>	<b>74</b>	<b>117</b>

\*Pearson chi-square P < 0.001; <sup>†</sup>Pearson chi-square P = 0.002.

**Table 9.** Accuracy of absolute and relative handgrip strength (HGS) for prediction of fear of falling among men

Absolute			
Sensitivity	{18/(18+28)}	0.39	39%
Specificity	{71/(4+71)}	0.94	94%
Positive predictive value (PPV)	{18/(18+4)}	0.81	81%
Negative predictive value (NPV)	{71/(28+71)}	0.71	71%
Positive likelihood ratio (LR+)	sensitivity/(1-specificity)	6.5	
Negative likelihood ratio (LR-)	(1-sensitivity)/specificity	0.64	
Relative			
Sensitivity	{12/(12+31)}	0.27	27%
Specificity	{69/(5+69)}	0.93	93%
Positive predictive value (PPV)	{12/(12+5)}	0.70	70%
Negative predictive value (NPV)	{69/(31+69)}	0.69	69%
Positive likelihood ratio (LR+)	sensitivity/(1-specificity)	3.85	
Negative likelihood ratio (LR-)	(1-sensitivity)/specificity	0.78	

**Table 10.** Accuracy of absolute and relative handgrip strength (HGS) for prediction of fear of falling among women

Absolute			
Sensitivity	{87/(87+204)}	0.29	29%
Specificity	{115/(42+115)}	0.73	73%
Positive predictive value (PPV)	{87/(87+42)}	0.67	67%
Negative predictive value (NPV)	{115/(204+115)}	0.36	36%
Positive likelihood ratio (LR+)	sensitivity/(1-specificity)	1.07	
Negative likelihood ratio (LR-)	(1-sensitivity)/specificity	0.97	
Relative			
Sensitivity	{65/(65+218)}	0.22	22%
Specificity	{141/(14+141)}	0.90	90%
Positive predictive value (PPV)	{65/(65+14)}	0.82	82%
Negative predictive value (NPV)	{141/(218+141)}	0.39	39%
Positive likelihood ratio (LR+)	sensitivity/(1-specificity)	2.2	
Negative likelihood ratio (LR-)	(1-sensitivity)/specificity	0.86	

**Table 11.** Absolute\* and relative<sup>†</sup> handgrip strength (HGS) in relation to fear of falling among women

	Fear of falling		Total
	Present	Absent	
Absolute HGS < 21.7 kgf	87	42	129
Absolute HGS > 21.7 kgf	204	115	319
<b>Total</b>	<b>291</b>	<b>157</b>	<b>448</b>
Relative HGS (BMI) < 0.66 kgf	65	14	79
Relative HGS (BMI) > 0.66 kgf	218	141	359
<b>Total</b>	<b>283</b>	<b>155</b>	<b>438</b>

\*Pearson chi-square  $P = 0.48$ ; <sup>†</sup>Pearson chi-square  $P < 0.001$ .

The evidence from this study highlights the imminent hazard that surrounds the oldest age group (80 years and over). These individuals showed the highest fear of falling, which may have impacted on their physical performance, which was the worst among the groups. It is difficult to predict when this cascade effect will begin, but it is crucial to implement interventions addressing physical and psychosocial issues, in order to face up to these conditions and thus promote health.

The values for handgrip strength that we found here were similar to those shown by Yoshimura et al.<sup>18</sup> However, the subjects in their study performed better regarding walking speed. Importantly, in their study, the subjects were categorized into decades of age and walking speed was measured along a 6-m path.

The Asian Working Group for Sarcopenia (AWGS) recommended using the lowest 20<sup>th</sup> percentile of handgrip strength of the study population as the cutoff value for low strength, due to the lack of outcome-based cutoff values. Thus, they suggested values of < 26 kgf for men and < 18 kgf for women.<sup>2</sup> Similarly, the European Working Group on Sarcopenia in Older People (EWGSOP) suggested < 30 kgf for men and < 20 kgf for women as cutoff values.<sup>3</sup> In our study, we found cutoffs of 30 kgf for Brazilian men and 21.7 kgf for Brazilian women, for absolute handgrip strength values. Although we were unable to contribute cutoff values for walking speed among Brazilian older adults at this time, both of these previous studies (AWGS and EWGSOP) recommended use of < 0.8 m/s as the cutoff for slow walking performance.<sup>2,3</sup>

Concerns have been raised regarding the influence of body mass on the relationships between performance, strength and muscle mass. These were raised especially by the Foundation for the National Institutes of Health (FNIH Sarcopenia Project), a large sample study that used multiple existing data sources to identify criteria for clinically relevant weakness and low lean mass.<sup>5,19,20</sup> Therefore, we performed several analyses to clarify the need to adjust handgrip strength and muscle mass for body mass. Through this, we found cutoffs for relative handgrip strength adjusted for BMI of 1.07 for men and 0.66 for women. The definitions for weakness suggested from the FNIH Sarcopenia Project were ratios < 1.0 for

men and < 0.56 for women.<sup>20</sup> The necessity for this adjustment will be further discussed below.

Regarding the TUG, Bohannon (2006) conducted a descriptive meta-analysis and found mean values according to age (60 to 69, 70 to 79 and 80 to 99 years) of 8.1 seconds (95% CI = 7.1-9.0), 9.2 seconds (95% CI = 8.2-10.2) and 11.3 seconds (95% CI = 10.0-12.7), respectively.<sup>11</sup> Individuals whose performance was outside the limits of these confidence intervals could be considered to have worse-than-average performance. These values were within the range that we found in our study. Furthermore, considering healthy Japanese individuals aged 60 years and over, Kamide et al. found that the weighted mean for TUG with maximum effort was 6.60 seconds (95% CI = 6.18-7.02) and that at the usual pace it was 8.86 seconds (95% CI = 7.99-9.72).<sup>21</sup> This was certainly faster than has been found in other populations.

The data of our study showed through specific tests that physical performance declined for both genders as age increased, but that the changes in skeletal muscle depended on the adjustment applied. The ASM cutoff values (adjusted for BMI) that were identified among older adults according to gender were 0.85 for men and 0.53 for women. Interestingly, the values proposed by the FNIH Sarcopenia Project were 0.789 and 0.512, for men and women, respectively.<sup>5</sup> We also found that adjustments for BMI were the best approach in relation to both genders. Therefore, we suggest that these cutoffs should be used to screen older adults of both sexes for higher risk of disability, in relation to fear of falling. These values provide a more realistic approach towards Brazilian older individuals.

Because of the adjustments to the data that we implemented, our results are not directly comparable with other proposed definitions for low ASM or sarcopenia. Initially, both the EWGSOP and AWGS groups suggested the approach of using  $-2$  SD of ASM in young individuals as a cutoff point for muscle mass.<sup>2,3</sup> However, low muscle mass alone is not consistently associated with adverse health outcomes,<sup>5</sup> which thus poses the challenge of implementing new approaches. Hence, the methodology adopted in our study limited our ability to make comparisons, but it stimulates other researchers to provide more suitable and comparable data.

Considering the role of body mass, it differed according to gender. In men, the AUC was slightly smaller for relative than for absolute handgrip strength. However, in women, relative handgrip strength showed better results. Interestingly, Alley et al. reported a similar finding.<sup>19</sup> In our study, this was seen despite our small sample size in the men's group and with a different outcome-based variable. It remains unclear why this occurred. BMI would be more important for women than for men.

To our knowledge, this was the first study to provide reference data and cutoff values adjusted according to body mass, for Brazilian older adults. We expect that these data will be useful both for clinicians within their practice and for researchers, who

will now be able to use Brazilian data regarding physical function and muscle mass in older adults.

We provided several adjustments to the data, but for consistency, we encourage researchers to use ASM adjusted for BMI and, according to convenience, to choose between absolute and relative handgrip strength adjusted for BMI, for both men and women, or even different types of indicators for each gender. For walking speed, a cutoff value  $< 0.8$  m/s, as previously suggested,<sup>2,3,5</sup> can be applied within both research and clinical practice to identify mobility impairment. Values for physical function tests and other variables can be used as references, according to age categories, as we presented in this study.

The limitations of this study included: (i) its cross-sectional design, which did not allow determination of a cause-effect relationship between the variables; (ii) the small number of older male subjects; (iii) the retrospective nature of the data on occurrences of falls, which may have been biased; and (iv) the use of fear of falling, and no other disability condition or mortality, as the outcome. Longitudinal analyses are preferable over cross-sectional designs and are appropriate for establishing clinical diagnostic cutoff values.<sup>5</sup> Moreover, even though mortality or other disability outcomes seem more representative for sarcopenia, fear of falling was highly associated with sarcopenia among older adults,<sup>22</sup> as previously verified, thus justifying its use as an outcome. We suggest that future studies should recruit larger numbers of male subjects and use different sampling fields and alternative methods for investigating body composition, such as dual-energy x-ray absorptiometry. In addition, longitudinal studies using disability or mortality as an outcome are necessary in order to determine optimal cutoffs for ASM, handgrip strength and walking speed.

In summary, we identified age-related decline in physical function and changes in body composition and anthropometric measurements. Moreover, cutoff values for handgrip strength (absolute: men  $< 30$  kgf; women  $< 21.7$  kgf; and relative: men  $< 1.07$ ; women  $< 0.66$ ) and for ASM (ASM adjusted for BMI: men  $< 0.85$ ; women  $< 0.53$ ), in relation to fear of falling among Brazilian older adults were also provided. Further analyses also suggested that adjustment for BMI may influence how the data can be interpreted. The cutoff value for walking speed was established as  $< 0.8$  m/s, as previously recommended. In future studies, we intend to evaluate the capacity of these cutoff values to identify individuals who are in a vulnerable condition, especially regarding low quality of life and frailty.

## CONCLUSION

The values for physical function tests and other variables, presented according to age groups, highlight the hazards that surround the most elderly individuals. These data are useful references both for clinicians within practice and for researchers. Moreover, ASM adjusted for BMI was the best approach, while adjustment of

handgrip strength varied according to gender. We recommend use of ASM adjusted for BMI and to choose either absolute handgrip strength or relative handgrip strength (adjusted for BMI), for both men and women, according to study needs.

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# Relationship between total and segmental bone mineral density and different domains of physical activity among children and adolescents: cross-sectional study

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## KEY WORDS:

Bone density.  
Leisure activities.  
Motor activity.  
Sports.

## ABSTRACT

**BACKGROUND:** This study aimed to investigate the relationship between total and segmental bone mineral density (BMD) and physical activity (PA) in different domains (school, leisure and sports) among adolescents and children.

**DESIGN AND SETTING:** Cross-sectional study in the Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP).

**METHODS:** The study sample consisted of 173 children and adolescents ( $10.31 \pm 1.87$  years). The BMDs for the whole body (WB) and the regions of the trunk and legs were measured using dual energy X-ray absorptiometry (DXA). PA was measured using the Baecke questionnaire. A regression model was used to analyze the relationship between all the BMDs and the different domains of PA.

**RESULTS:** 41.5% of the adolescents had high percentages of body fat. Regarding the comparison between physically active and insufficiently active adolescents, there were no statistically significant differences in any BMD variables ( $P > 0.05$ ). The BMD of the legs showed positive relationships with the total PA ( $\beta = 0.009$ ;  $P = 0.013$ ) and sports PA ( $\beta = 0.010$ ;  $P = 0.049$ ) after insertion of the confounders. Similarly, the WB BMD showed the same relationships (total PA:  $\beta = 0.005$ ;  $P = 0.045$ ; and sports PA:  $\beta = 0.008$ ;  $P = 0.049$ ). No relationship was found between leisure and school PA and any of the BMDs ( $P > 0.05$ ).

**CONCLUSION:** The results indicated that practice of sport was related to higher BMD values, independent of sex, age and body fatness.

## INTRODUCTION

Development of human tissue, including bone tissue, is determined by biological events during childhood and adolescence.<sup>1</sup> Bone mineral density (BMD) represents the amount of inorganic material (calcium and phosphorus) stored in the bones, which varies over the course of life. It can be measured either for the whole body or in segments.<sup>1,2</sup> Low BMD values are related to development of osteoporosis, mainly in later life, but also in pediatric populations.<sup>2</sup> Bone health in adulthood is determined by bone development over the course of early life, which can be affected by a large variety of variables, such as genetics, nutrition, hormone action, biological maturation and physical activity (PA).<sup>3,4</sup>

PA exerts significant influence on BMD accrual during growth,<sup>4</sup> which can be categorized into domains (school, leisure and sports). School PA denotes activities performed during school activities,<sup>5,6</sup> while leisure PA denotes activities performed during free time.<sup>7-9</sup> Moreover, in young populations, sport PA can itself be considered to be a PA domain.<sup>10-12</sup>

PA at vigorous intensity, including mechanical loading on the bones, positively affects bone mass due to:

1. Muscle action, which promotes high load and stress on the bones, thereby affecting and modifying bone strength and geometry;
2. The rate of bone turnover, which is modulated by the action of osteoblast (formation) and osteoclast (resorption) systems, which in turn promote significant gains in BMD.<sup>13</sup>

In this way, PA can have a greater influence on some specific BMD segments in the body.<sup>3,11</sup> The BMD of the legs comprises one component of weight-bearing joints and may be indicative of a specific site where bone-loading occurs and tends to have greater impact. On the other hand, upper limbs are used more specifically in activities such as combat sports<sup>11</sup> and gymnastics.<sup>14</sup> Thus, it appears to be of interest to investigate the effect of PA on BMD in different body segments.

Moreover, although BMD and PA have been correlated in studies involving organized physical activity (physical exercise and types of sport),<sup>15</sup> there are fewer data on the relationship between bone health and leisure PA. The absence of data on this issue is more relevant among young people, because important confounders (body fat, age and gender) affect growth and it is not clear whether the impact of PA is independent of these confounders.

## OBJECTIVE

Thus, the objectives of this study were to compare BDM (both total and segmental), between physically active and insufficiently active adolescents, and to evaluate the relationship between the practice of physical activities in different domains (school, sports and leisure), and whole-body and appendicular BMD.

## METHODS

### Compliance with ethical standards

This study was approved by the ethics board of Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), Presidente Prudente campus (procedural number: 26702414.0.0000.5402). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or the national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent was obtained from all parents before the adolescents were included in the study.

### Study design and subjects

This was a cross-sectional study evaluating the level of physical activity and BDM among adolescents in Presidente Prudente at Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP).

The study sample was composed of 173 adolescents, aged between 10-14 years (mean = 11.68 years; standard deviation, SD = 1.44), who formed part of a Brazilian social project with activities at a philanthropic institution in Presidente Prudente, state of São Paulo, Brazil. All the children and adolescents of this social project were invited to participate in the study and those who accepted formed part of the study sample. All participants presented a consent statement signed by a parent or guardian, authorizing them to participate in this study.

### Anthropometric measurements and biological maturation

Body mass was obtained using a digital scale accurate to 0.1 kg. Height was measured using a fixed stadiometer accurate to 0.1 cm, with a maximum length of two meters. From these measurements, body mass index (BMI) was calculated and the z score was generated. Leg length and seated height were measured using standardized techniques. These measurements were used to calculate the maturity offset, which denotes the time (years) from/to the age of peak height velocity (APHV), which is an important maturational event.<sup>16</sup>

### Bone mineral density

Dual energy X-ray absorptiometry (DXA) was used to assess BDM. DXA can be used to analyze the whole-body, trunk region and leg BMDs (WB BDM, trunk BMD and leg BDM, respectively) in g/m<sup>2</sup>, along with the percentage body fat (%BF). The equipment used was the Lunar-DPX-NT model (General Electric, GE). The results were expressed as means, which were calculated using specific software supplied with the equipment.

Body fat levels were classified high if they were above 25% and above 30% for male and female adolescents respectively, in accordance with the cutoffs proposed by Williams et al.<sup>17</sup>

### Physical activity

Habitual PA was assessed using the questionnaire developed by Baecke et al.,<sup>10</sup> which has been validated for use among Brazilian adolescents.<sup>18</sup> This questionnaire assesses habitual PA according to three different domains: school, leisure and sports outside school. The school score was assessed from questions relating to the amount of time spent performing the following activities during school time: sitting, standing, walking, lifting heavy loads, fatigue and sweating. The leisure PA score specifically asked about time spent on watching television, walking, cycling and active transportation (via walking and/or cycling). Finally, the sport PA score was calculated by asking about which two specific sports the adolescent participated in most frequently, their number of hours per week and months per year of participation and their degree of sweating; and by making comparisons of PA levels with other individuals of the same age. The total score was calculated by adding together the individual scores for school, leisure and sport PA.

Moreover, this questionnaire had previously been validated against the gold standard method (doubly labeled water) for measurement of PA.<sup>19</sup> Children and adolescents located in the highest quartile of total PA (Q4) were considered to be physically active, while children and adolescents in the intermediate quartiles (Q2 and Q3) were classified as moderately active and those in the lowest quartile (Q1) were classified as inactive.

### Statistical analysis

The data were subjected to the Kolmogorov-Smirnov test to verify normality. If the distribution was found to be normal, the variables of the sample were characterized in terms of the mean and standard deviation. The Pearson correlation was used to examine the relationship between PA and BMD values among the adolescents. Regression models were used to evaluate the relationship between BMD and PA (treated in this statistical analysis in the continuous form) either with each PA domain or with the total PA, using independent variables. In the first multivariate analysis, the variables of sex and age were inserted in order to eliminate possible confounding factors when analyzing the relationships between the different PA domains and trunk BMD, leg BMD and WB BMD. In the second multivariate model, %BF assessed by means of DXA and maturation was inserted to verify whether the relationships between the PA domains and trunk BMD, leg BMD and WB BMD remained. Firstly, the relationship between the different domains of physical activity and bone mineral density was evaluated separately; and secondly, these domains were inserted simultaneously in order to verify whether any of the domains overlapped on the others (e.g. situations in which physical activity in school and sports practice were correlated with higher bone mineral density of the legs, both when analyzed separately and when inserted simultaneously). The statistical significance level adopted was 5%.

### RESULTS

The DXA evaluation showed that the percentage of the adolescents with high levels of body fat ( $\geq 25\%$  for boys and  $\geq 30\%$  for girls) was 41.5%. Girls had a higher percentage of body fat than boys: 38.0% and 49.5% respectively. **Table 1** shows the characteristic information of the sample according to the PA level (physically active, moderately or inactive).

The following PA correlations among the young people were not significant: between PA at school and trunk BMD ( $r = 0.14$ ;  $P = 0.063$ ); between PA in sports activities outside the school environment and trunk BMD ( $r = 0.13$ ;  $P = 0.077$ ); and between PA during leisure time and trunk BMD ( $r = 0.06$ ;  $P = 0.430$ ). **Table 2** shows the multivariate analysis information on the relationship between BMD and the different physical activity domains. No significant relationships between the different domains of physical activity and trunk BMD were observed.

PA performed by the young people at school was not significantly related to leg BMD ( $r = 0.13$ ;  $P = 0.075$ ). However, PA during leisure time showed a significant relationship with leg BMD ( $r = 0.21$ ;  $P = 0.005$ ) and practicing sports activities outside the school was significantly associated with leg BMD ( $r = 0.20$ ;  $P = 0.008$ ). In **Table 3**, in the multivariate analysis, only the sports practice and total PA were related to higher leg BMD.

PA at school was not significantly related to WB BMD ( $r = 0.16$ ;  $P = 0.111$ ). PA in sports was related to WB BMD ( $r = 0.18$ ;  $P = 0.003$ ) and PA during leisure time did not show any significant relationship with WB BMD ( $r = -0.13$ ;  $P = 0.079$ ). Sports practice and total PA were correlated with higher WB BMD in the multivariate analysis. This information is shown in **Table 4**.

The sum of the three PA domains was unrelated to trunk BMD ( $r = 0.06$ ;  $P = 0.418$ ), but this sum had statistically significant relationships with leg BMD ( $r = 0.17$ ;  $P = 0.027$ ) and WB BMD ( $r = 0.15$ ;  $P = 0.048$ ).

After all adjustments, with the variables entered separately in the multivariate models, it was observed that PA at school and during leisure time was not related to the different BMDs analyzed ( $P > 0.05$ ). Sports practice among the adolescents was significantly related to higher leg BMD ( $\beta = 0.012$ ; 95% confidence interval, CI = 0.001-0.023;  $P = 0.028$ ) and WB BMD ( $\beta = 0.009$ ; 95% CI = 0.001-0.017;  $P = 0.036$ ) (**Tables 2, 3 and 4**). Regarding the total PA, which was the sum of the three PA domains, we found positive relationships with leg BMD ( $\beta = 0.009$ ; 95% CI = 0.002-0.016;  $P = 0.013$ ) and WB BMD

**Table 1.** Characteristics of the subjects according to physical active level

	Inactive Mean (SD)	Moderately active Mean (SD)	Sufficiently active Mean (SD)	P
Age (years)	10.02 (1.92)	10.45 (1.86)	10.30 (1.94)	0.479
Weight (kg)	42.47 (16.83)	42.50 (13.18)	44.46 (13.39)	0.733
Height (cm)	144.50 (12.41)	146.61 (11.68)	147.32 (13.17)	0.528
BMI (kg/m <sup>2</sup> )	19.76 (4.98)	19.35 (3.99)	20.23 (4.75)	0.565
Z-score for BMI	0.06 (1.13)	-0.06 (0.83)	0.13 (1.06)	0.572
Body fat (%)	25.94 (12.86)	25.08 (11.82)	25.73 (15.80)	0.567
Trunk BMD (g/cm <sup>2</sup> )	0.76 (0.09)	0.77 (0.08)	0.79 (0.07)	0.231
Leg BMD (g/cm <sup>2</sup> )	0.95 (0.13)	0.93 (0.12)	1.03 (0.12) <sup>a</sup>	0.009
WB BMD (g/cm <sup>2</sup> )	0.93 (0.09)	0.95 (0.07)	0.99 (0.07) <sup>a</sup>	0.001

SD = standard deviation; BMI = body mass index; BMD = bone mineral density; WB = whole body. <sup>a</sup>statistically significant in relation to the inactive group.

**Table 2.** Relationship between trunk bone mineral density and different physical activity domains

PA domain	Adjusted for age and sex			Adjusted for age, sex, PGR and %BF		
	Beta	95% CI	P	Beta	95% CI	P
<b>Entered separately in the regression model</b>						
Total	0.002	(-0.004; 0.008)	0.445	0.001	(-0.04; 0.007)	0.608
School	0.000	(0.000; 0.001)	0.084	0.001	(0.000; 0.001)	0.158
Sport	0.006	(-0.003; 0.015)	0.205	0.007	(-0.001; 0.015)	0.101
Leisure	-0.004	(-0.015; 0.007)	0.440	-0.001	(-0.010; 0.009)	0.883
<b>Entered simultaneously in the regression model</b>						
School	0.000	(0.000; 0.001)	0.130	0.000	(0.000; 0.001)	0.243
Sport	0.006	(-0.004; 0.015)	0.250	0.006	(-0.002; 0.013)	0.136
Leisure	-0.005	(-0.016; 0.006)	0.347	-0.002	(-0.012; 0.007)	0.671

%BF = body fat; PA = physical activity; PGR = peak growth rate; 95% CI = 95% confidence interval; SD = standard deviation.

( $\beta = 0.005$ ; 95% CI = 0.000-0.011;  $P = 0.045$ ). When the variables were entered simultaneously in the regression model, only the relationships between the sports domain and leg BMD ( $\beta = 0.010$ ; 95% CI = 0.001-0.023;  $P = 0.049$ ) and WB BMD ( $\beta = 0.008$ ; 95% CI = 0.001- 0.015;  $P = 0.049$ ) remained significant.

## DISCUSSION

The relationship between PA in different domains (school, sports and leisure) and whole-body and segmental BMD measured by means of DXA among children and adolescents was examined. After adjusting for confounding variables (age, sex and %BF), the analysis showed that sports practice had a positive relationship with total and segmental BMD, and with total PA analyzed as the sum of the three different PA domains.

PA practice appears to be essential for maintaining bone health.<sup>20</sup> However, studies have demonstrated that only physical activities of moderate and vigorous intensity benefit BMD.<sup>5,13</sup> In this respect, our study showed that the sufficiently active adolescents did not show higher total and segmented BMD than that

of the insufficiently active (Table 1). Corroborating our findings, Gracia-Marco et al.<sup>21</sup> found that children classified as physically active showed no differences in BMD, compared with sedentary individuals. Their categorization took total PA into account, which may have included sedentary and light activities, which have a less positive relationship regarding addition of BMD.<sup>22</sup>

The present study demonstrated that total PA (i.e. the sum of school, sports and leisure PA) presented a positive relationship with WB BMD, trunk BMD and leg BMD, even after all statistical adjustments. Corroborating this, Tobias et al.<sup>22</sup> showed that practicing moderate to vigorous PA had a positive correlation with the BMD of the lower limbs after adjustments for height, lean body mass and body fat. Neville et al.<sup>23</sup> found data similar to ours, i.e. that the sum of PA, derived from the Baecke questionnaire, was positively associated with increases in lumbar spine and femoral neck BMD. However, the participants in the sample of Neville et al.<sup>23</sup> were 15 years or over, while it has been reported that the greatest accrual of bone mass occurs at around 13 and 11 years, respectively, in boys and girls.<sup>11</sup> Furthermore, the Baecke questionnaire was used only to evaluate the total PA, thus missing a lot of information regarding the different PA domains (school, sports and leisure).

Therefore, we investigated the relationships of all PA domains with total and segmental BMD. It was found that physical activity at school showed no relationship with total or segmental BMD. Agreeing with our results, Heidemann et al.<sup>5</sup> found from a two-year follow-up that increased physical activity at school (e.g. the number of days of physical education) did not give rise to any significant increase in BMD. Valdimarsson et al.<sup>6</sup> found that girls who engaged in more than 3 hours of physical education at school per week during a one-year follow-up did not present higher total and leg BMD than those at a traditional school (1 hour of physical education per week). These findings suggest that physical activity performed only in a school environment is insufficient to generate increases in BMD. Since no details on the type of activities performed in these interventions were reported in those studies, we assume that these findings were due to low weight-bearing activities in the interventions.

On the other hand, some studies have demonstrated beneficial effects on BMD sites from interventions during school time, even after three years.<sup>24</sup> In the study by Meyer et al.,<sup>24</sup> the physical education classes were composed of a multi-component PA intervention that included daily physical education with at least 10 minutes of jumping or strength-training exercises of various intensities. A similar protocol was used by Heidemann et al.,<sup>5</sup> comprising increased numbers of physical education classes, but the results were different. In their study, the adolescents who participated in the nine-month intervention program demonstrated increased total BMD. However, comparisons between the results from these studies showed that there were some limitations regarding the type,

**Table 3.** Relationship between leg bone mineral density and different physical activity domains

PA domain	Adjusted for age and sex			Adjusted for age, sex, PGR and %BF		
	Beta	95% CI	P	Beta	95% CI	P
<b>Entered separately in the regression model</b>						
Total	<b>0.010</b>	<b>(0.002;0.018)</b>	<b>0.011</b>	<b>0.009</b>	<b>(0.002;0.016)</b>	<b>0.013</b>
School	0.001	(0.000;0.001)	0.110	0.001	(0.000;0.001)	0.198
Sport	0.012	(-0.001;0.024)	0.066	<b>0.012</b>	<b>(0.001;0.023)</b>	<b>0.028</b>
Leisure	0.008	(-0.006;0.023)	0.261	0.013	(0.000;0.026)	0.055
<b>Entered simultaneously in the regression model</b>						
School	0.000	(0.000;0.001)	0.164	0.000	(0.000;0.001)	0.294
Sport	0.010	(-0.003;0.022)	0.137	<b>0.010</b>	<b>(0.001;0.023)</b>	<b>0.049</b>
Leisure	0.007	(-0.049;0.016)	0.360	0.011	(-0.002;0.024)	0.103

%BF = body fat; PA = physical activity; PGR = peak growth rate; 95% CI = 95% confidence interval; SD = standard deviation.

**Table 4.** Relationship between whole body bone mineral density and different physical activity domains

PA domain	Adjusted for age and sex			Adjusted for age, sex, PGR and %BF		
	Beta	95% CI	P	Beta	95% CI	P
<b>Entered separately in the regression model</b>						
Total	<b>0.006</b>	<b>(0.000;0.012)</b>	<b>0.039</b>	<b>0.005</b>	<b>(0.000;0.011)</b>	<b>0.045</b>
School	0.001	(0.000;0.001)	0.179	0.000	(0.000;0.001)	0.335
Sport	0.008	(-0.001;0.017)	.0074	<b>0.009</b>	<b>(0.001;0.017)</b>	<b>0.036</b>
Leisure	0.001	(-0.009;0.012)	0.813	0.004	(-0.005;0.014)	0.400
<b>Entered simultaneously in the regression model</b>						
School	0.000	(0.000;0.001)	0.273	0.001	(0.000;0.001)	0.493
Sport	0.007	(-0.002;0.016)	0.113	<b>0.008</b>	<b>(0.001;0.015)</b>	<b>0.049</b>
Leisure	-0.001	(-0.010;0.010)	0.995	0.003	(-0.007;0.012)	0.598

%BF = body fat; PA = physical activity; PGR = peak growth rate; 95% CI = 95% confidence interval; SD = standard deviation.

frequency and duration of PA and pubertal maturation, which makes it difficult to establish a pattern in the relationship between school PA and BMD.

In our investigation on the relationship between leisure PA and BMD sites, it was found that school PA was unlikely to be sufficient to increase total and segmental BMD. In the Baecke questionnaire, there are two important questions in this section that address how long adolescents spend walking and/or cycling. Thus, adolescents who are active with regard to leisure PA must spend more time on these activities. Park et al.<sup>9</sup> found that the practice of regular walking was not positively correlated with total or segmental BMD in adolescents. Corroborating this, in the study by Deere et al.<sup>7</sup> adolescents who practiced running or high-impact activities presented higher values for hip BMD. In contrast, the practice of jogging showed little benefit at the BMD sites. Another type of leisure PA considered in the questionnaire was cycling. A large number of studies have demonstrated that the practice of cycling is insufficient to increase total and segmental BMD.<sup>8,15</sup> These results demonstrated that physical activity performed without or with little weight-bearing showed no benefits at the BMD sites.

Moreover, in our study, the practice of sports PA was related to whole-body and leg BMD, even after introduction of confounding variables in the multivariate model. Corroborating this, Nasri et al.<sup>11</sup> found that adolescents who practiced combat sports had higher values for total hip and lumbar spine (L2-L4) BMD, compared with sedentary individuals. Silva et al.<sup>12</sup> found that adolescents who engaged in practicing sports such as soccer and tennis had greater BMD than the control group. On the other hand, adolescents who practiced swimming did not present increased BMD.

Furthermore, sports can be categorized as vigorous PA. It is known that vigorous PA promotes gains in BMD.<sup>11</sup> In this regard, Cardadeiro et al.<sup>13</sup> found that an additional 10 minutes of vigorous PA per day suggested a 1-2% increase in BMD in children. These findings are consistent with the results from a 15-year monitoring epidemiological study.<sup>25</sup> Moreover, Heidemann et al.<sup>5</sup> found similar findings in their two-year follow-up. Adolescents who increased their amounts of high-intensity PA had greater gains in BMD than did those with lower levels.

These positive relationships between PA, especially sports, and total and segmental BMD can be explained by the action of osteocytes, which are embedded within the mineralized bone. In response to mechanical loads or microlesions, these provide signals to osteoclasts, which carry out resorption. Moreover, it is known that in pre-pubertal children, the osteogenic process is more sensitive to the mechanical load in the bone, and this can augment the duration of the peak bone mass.<sup>4,16</sup> Taken together, these data suggest that performing sport during adolescence shows great benefits for bone mass, and thus, may prevent development of early osteoporosis.<sup>26</sup>

Despite the importance of the results found here, it is important to mention some limitations. The cross-sectional design does not allow any consideration of the effect of time on these adolescents and thus does not allow causal inferences. Some of the results were borderline, meaning that the sample size was probably small. Measuring PA by means of the questionnaire of Baecke et al.<sup>10</sup> may involve self-reporting errors, since it depends on the reviewers' perception. However, among the questionnaires commonly used in epidemiological studies, use of the one described by Baecke et al.<sup>10</sup> seems to be a good strategy for mitigating the limitations inherent in questionnaires, since it has a high correlation with the gold standard for estimating PA. Furthermore, use of this questionnaire allowed us to analyze the different domains of PA, thereby indicating how to increase BMD and where public policy should act to provide the means for practicing PA.

## CONCLUSION

In summary, in this sample composed of adolescents, sport practice was correlated with higher BMD values, independent of sex, age and body fatness.

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# Risk and protection factors for self-reported hypertension and diabetes in João Pessoa, Brazil. The VIGITEL survey, 2014. A cross-sectional study

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## KEY WORDS:

Chronic disease.  
Hypertension.  
Diabetes mellitus.  
Risk factors.  
Cross-sectional studies.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Chronic diseases are the main cause of death among adults and are responsible for most outpatient and hospital care expenses in Brazil. The objective here was to determine the prevalence of hypertension and diabetes and to analyze the associations with risk and protection factors among adults.

**DESIGN AND LOCAL:** Cross-sectional study in a state capital in northeastern Brazil.

**METHODS:** Data on adults of both sexes aged  $\geq 45$  years who were interviewed in the Vigitel telephone survey in 2014 were analyzed. Prevalence ratios were estimated using Poisson regression, to identify associated factors.

**RESULTS:** Among women, the prevalence of hypertension was 48.4% and of diabetes, 12.7%; among men, the prevalences were 41.9% and 13.8%, respectively. Multivariate analysis showed that for women, age group  $\geq 65$  years, overweight, self-assessed poor health and dyslipidemia remained associated with higher prevalence of hypertension. For men, overweight and self-assessed poor health remained associated with higher prevalence of hypertension. Regarding diabetes, in the multivariate model for women, age group 55-64 years, schooling level between zero and four years and no regular consumption of beans remained associated with higher prevalence. For men, age groups 55-64 years and  $\geq 65$  years and being married or in a stable partnership were associated with higher prevalence of diabetes.

**CONCLUSIONS:** The results indicated that the prevalences of hypertension and diabetes were high and that preventable factors were associated with this situation, thus providing support for public policies aimed towards coping with this.

## INTRODUCTION

The four major noncommunicable diseases are cardiovascular diseases, diabetes, neoplasms and chronic respiratory diseases. These diseases have several common risk factors, which can be classified as modifiable and non-modifiable. The modifiable risk factors include smoking, abusive consumption of alcoholic beverages, excess body weight, unhealthy eating habits, sedentary lifestyle and metabolic abnormalities such as dyslipidemias. The non-modifiable risk factors are heredity, race, sex and age.<sup>1</sup> The Global Burden of Disease (GBD)<sup>2</sup> study, coordinated by the Institute of Metrics and Health Assessment (IHME) of the University of Washington (United States) showed that in Brazil, between 1990 and 2010, there were changes in the rankings among the ten leading causes of death. Among these causes of years of life lost due to premature death (YLLs), diabetes and hypertension increased by more than 40% over this period. The five leading causes of years of life lost due to death or disability (DALYs) among women were depression, ischemic heart disease, low back pain, cerebrovascular disease and diabetes; and among men, homicide, ischemic heart disease, car accidents, low back pain and cerebrovascular disease. Also according to this study,<sup>2</sup> the risk factors that most contributed towards premature death and loss of health among men and women in Brazil in 2010 were inadequate diet, high blood pressure, overweight and altered fasting glycemia.

In the northeastern region of Brazil, data from 2014 on the major groups of causes of death that were reported by the Department of Informatics of the Brazilian National Health System

(DATASUS)<sup>3</sup> showed that diseases of the circulatory and endocrine systems and nutritional and metabolic diseases corresponded, respectively, to proportions of deaths of 27.56% and 7.52%, in comparison with the total number of deaths from all causes. In João Pessoa, the state capital of Paraíba, which was the subject of the present study, data from 2014 also reported by DATASUS<sup>3</sup> showed that diseases of the circulatory and endocrine systems and nutritional and metabolic diseases corresponded, respectively, to proportions of deaths of 27.48% and 6.67%, in comparison with the total number of deaths from all causes.

Diabetes is a highly incapacitating disease that can cause diabetic retinopathy, amputations, nephropathies, cardiovascular and encephalic complications, among other conditions. It can impair individuals' functional capacity, autonomy and quality of life, thus resulting in high social and financial costs for society and for these individuals and their families.<sup>4</sup>

Hypertension is considered to be both a chronic disease and a risk factor for other diseases and chronic conditions, such as chronic kidney disease and diabetes, among others. This gives it greater prominence as these individuals' health conditions worsen, thus contributing towards loss of quality of life, early lethality of diseases and high costs for social and healthcare systems. It has a multifactorial nature, with an asymptomatic course in many cases, which means that this diagnosis is neglected and, consequently, so is treatment. In addition, hypertension is highly prevalent in Brazil and in the world, thus representing a great challenge for public health.<sup>5,6</sup>

A study carried out on the adult population of Campinas,<sup>7</sup> state of São Paulo, showed that there were significant differences in the prevalences of risk and protection factors for chronic diseases according to gender. The prevalences of smoking, former smokers, alcohol abuse, overweight, obesity and free-time physical activity were higher among men; among women, healthier eating habits and dyslipidemia were more prevalent.

Chronic diseases are responsible for the greatest proportion of the burden of diseases diagnosed in Brazil and present significant modifiable risk factors. The impact of these diseases and their risk factors varies according to gender and the level of development of the different regions of the country. Moreover, chronic diseases are highly prevalent among people aged 45 years and over.

Because very few studies on hypertension and diabetes have been conducted in João Pessoa, the aims of the present study were to ascertain the prevalence of these diseases and to identify and measure the independent effects of risk and protection factors relating to the presence of previous medical diagnoses of these diseases, as reported by adults in this municipality.

## OBJECTIVE

The objectives of this study were to ascertain the prevalence of hypertension and diabetes and to identify the relationships

of sociodemographic and behavioral characteristics, food consumption characteristics and health indicators towards the presence of previous medical diagnoses of these two chronic diseases, as reported by adults, stratified according to sex, in a state capital in northeastern Brazil.

## METHODS

This was a cross-sectional, population-based, epidemiological study that used data from the Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone (Vigitel) survey. The project for implementing Vigitel was approved by the National Ethics Committee for Research on Human Beings (CONEP) of the National Health Council (CNS), Ministry of Health, under report no. 355.590, of June 26, 2013, and under the certificate of presentation for ethics assessment (CAAE) no. 16202813.2.0000.0008. Since the project related to telephone interviews, the free and informed consent document was replaced by verbal consent that was obtained by the Ministry of Health at the time of the interview. To conduct the present study, the coordination office for non-transmissible diseases and health hazards of the Secretariat for Health Surveillance, Department of Health Situation Analysis, Ministry of Health, made data from Vigitel 2014 relating to João Pessoa (capital of the state of Paraíba) available to us.

Adults aged 45 years and over who were living in households in João Pessoa served by at least one landline telephone in the year 2014 were included. During that year, 1,517 adults aged 18 and over living in this city were interviewed as part of the Vigitel survey.<sup>8,9</sup> Out of this total, 867 interviews were conducted with adults aged 45 years and over, i.e. the target audience of the present study. These individuals comprised 566 females (65.28%) and 301 males (34.71%). This sample of 867 adults was weighted according to sex, age and schooling, in accordance with the methodology established for Vigitel, using the "rake" method,<sup>8-11</sup> thus making the data of this sample representative of the total adult population of this capital. Details of the sampling process and the weighting of Vigitel estimates, along with other details of the methodology used by this system can be seen in other published papers.<sup>8,9</sup> The electronic questionnaire used at the time of the interviews is available in the annual publication of results from Vigitel.<sup>9</sup>

The dependent variables analyzed in this study were the prevalence of hypertension and the prevalence of diabetes, as reported by adults who had previously received these medical diagnoses. They were defined by the percentages of adults who reported having a prior medical diagnosis as positive answers to the following questions, respectively: "Has any doctor ever told you that you have high blood pressure?"; and "Has any doctor ever told you that you have diabetes?".

The independent variables analyzed in this study were selected based on their importance for determining the total

burden of disease, as estimated by the World Health Organization for the Americas region.<sup>12</sup> They consisted of risk and protection indicators selected from Vigitel, and were grouped into: sociodemographic, behavioral, food consumption and health indicators. The sociodemographic variables were: age group (45-54, 55-64 or  $\geq 65$  years); marital status (single, married/stable partnership, widowed or separated/divorced); schooling level (0-4, 5-8, 9-11 or  $\geq 12$  years of study); and possession of health insurance (yes or no). The behavioral categories included: smokers (adults who reported being current smokers, regardless of the number of cigarettes, frequency and duration of smoking); former smokers (adults who reported being former smokers, regardless of time elapsed); and physically inactive individuals (adults who had not exercised during their free time within the last three months, were not performing any intense physical efforts at work, were not going to work/school on foot or by bicycle with a minimum journey time of 20 minutes and were not performing heavy cleaning in their homes). The food consumption variables were: regular consumption of fruits, vegetables and greens (on five or more days of the week); recommended consumption of fruits, vegetables and greens (five servings daily, on five or more days of the week); regular consumption of beans (on five or more days of the week); consumption of meat with excess fat (habit of consuming red meat with visible fat and/or chicken with skin); consumption of milk with full fat content (habit of consuming whole milk fat); regular consumption of soda or artificial juice (on five or more days of the week); regular consumption of sweets (on five or more days per week); replacement of lunch or dinner by snacks (seven or more times a week); and high salt intake (adults who considered that their salt intake was high or too high). The health indicators analyzed the following conditions: overweight, in terms of the body mass index (BMI); defined as body weight (kg) divided by square of height (m<sup>2</sup>), for which self-reported information on weight and height was used to calculate BMI and adults who presented BMI  $\geq 25$  kg/m<sup>2</sup> were considered to be overweight, as classified by the World Health Organization;<sup>13</sup> self-assessed poor/very poor health (adults who assessed their health as poor or very poor, in answer to the question "Would you rate your health as: very good, good, normal, poor, or very poor?"); and dyslipidemia (adults who reported having a previous medical diagnosis of dyslipidemia: high cholesterol or triglycerides).

All the analyses were performed using the Vigitel expansion factor, using the Stata survey procedure version 11 SE. Initially, Pearson chi-square association tests were performed to verify the existence of a statistical association between the independent variables and outcomes ( $P \leq 0.05$ ). Subsequently, the Poisson regression model was used to verify the existence of factors associated with arterial hypertension and diabetes. The variables that presented

$P \leq 0.20$  in the univariate analysis were considered for introduction into the multivariate model. The magnitudes of the associations found were measured using prevalence ratios (PR) with their respective 95% confidence intervals (95% CI).

## RESULTS

Data from 867 adults aged 45 years and over were analyzed. These comprised 566 women and 301 men, corresponding to 65.28% and 34.72% of the total sample, respectively. Another 271 adults were excluded because they were 18-44 years old. Most of these individuals were between 25-34 years old, had 9 to 11 years of educational attainment and had no health insurance.

Previous medical diagnoses of hypertension and diabetes were reported by 45.8% and 13.1% of the population, respectively, and there were no significant differences between the genders.

**Table 1** describes the sociodemographic, behavioral, food consumption and health indicators of the study population and the presence of hypertension and diabetes, stratified according to gender. Among the women, there was higher prevalence of hypertension in the age group  $\geq 65$  years (95% CI: 50.6-66.2) and among those who did not consume whole milk (95% CI: 46.8-59.9); those who were overweight (95% CI: 52.2-65.4); those who self-rated their health as poor/very poor (95% CI: 48.1-85.2); and those who reported having a medical diagnosis of dyslipidemia (95% CI: 55.6-71.3). Among the men, there was statistically significant higher prevalence of hypertension in the age group  $\geq 65$  years (95% CI: 39.1-62.2) and among those who reported consuming meats with excessive fat (95% CI: 17.6-43.6); those who were overweight (95% CI: 39.0-56.6); those who self-assessed their health as poor (95% CI: 64.2-97.6); and those who reported having a medical diagnosis of dyslipidemia (95% CI: 42.0-67.4).

There was higher prevalence of diabetes among women over 55 years old (95% CI: 11.0-26.2); among those with 0-4 years of education (95% CI: 11.8-29.5); among those who did not consume beans regularly (95% CI: 11.9-26.2); among those who did not replace lunch or dinner with snacks (95% CI: 10.3-17.7); and among those who were overweight (95% CI: 11.2-20.8). There was higher prevalence of diabetes among men in the age group of 55-64 years (95% CI: 13.5-39.9); among those who were married or were in a stable partnership (95% CI: 11.8-24.8); among those who reported being former smokers (95% CI: 12.0-32.1); and among those who were overweight (95% CI: 11.3-25.1) (**Table 1**).

**Table 2** shows the crude and adjusted analyses on factors associated with hypertension in women and men. The adjusted analysis relating to the women's data showed that the age group  $\geq 65$  years old, excessive body weight, self-rated poor health and a previous medical diagnosis of dyslipidemia remained independently associated with higher prevalence of hypertension. Consuming whole-fat

**Table 1.** Prevalences of hypertension and diabetes in the population, according to gender and sociodemographic, behavioral, food consumption and health indicator characteristics. João Pessoa, Paraíba, Brazil (2014)

Variables	Hypertension					Diabetes				
	Female sex		Male sex		Total P (%)*	Female sex		Male sex		Total P (%)*
	P (%)*	P-value <sup>†</sup>	P (%)*	P-value <sup>†</sup>		P (%)*	P-value <sup>†</sup>	P (%)*	P-value <sup>†</sup>	
<b>Sociodemographic indicators</b>										
<b>Age group</b>										
45-54 years	40.1		31.9		36.7	6.8		4.3		5.8
55-64 years	51.5	0.010	50.0	0.038	50.9	17.3	0.011	24.4	0.001	20.2
≥ 65 years	58.6		50.7		55.6	17.2		18.5		17.7
<b>Marital status</b>										
Single	38.7		36.9		38.1	9.2		0.6		6.3
Married/stable partnership	48.6	0.278	42.7	0.892	45.7	12.1	0.401	17.4	0.000	14.7
Widowed	49.9		49.7		49.9	18.1		4.6		16.9
Separated/divorced	57.5		39.1		51.0	15.5		3.8		11.4
<b>Education</b>										
≥ 12 years	42.2		35.0		39.4	5.8		15.1		9.3
9-11 years	45.4	0.298	46.5	0.544	45.8	10.2	0.048	13.2	0.889	11.3
5-8 years	48.6		36.4		44.0	14.0		11.3		13.0
0-4 years	56.2		45.3		51.2	19.1		15.6		17.5
<b>Possession of health insurance</b>										
Yes	45.5	0.337	49.5	0.105	47.0	10.4	0.277	16.7	0.387	12.7
No	50.5		37.7		45.2	14.0		12.2		13.2
<b>Behavioral indicators</b>										
<b>Smokers</b>										
No	49.4	0.092	42.0	0.950	46.7	12.4	0.414	13.3	0.686	12.7
Yes	31.2		41.4		38.1	18.4		16.2		16.9
<b>Former smokers</b>										
No	48.7	0.875	42.4	0.870	46.4	14.1	0.197	9.8	0.046	12.5
Yes	47.8		41.2		44.7	9.2		20.2		14.4
<b>Physically inactive</b>										
No	46.2	0.129	38.4	0.117	43.1	11.2	0.130	13.8	0.988	12.2
Yes	55.4		51.7		53.8	12.7		13.9		15.8
<b>Food consumption indicators</b>										
<b>Regular consumption of FVG</b>										
Yes	45.5	0.265	43.6	0.687	44.8	11.9	0.624	13.7	0.981	12.5
No	51.4		40.7		46.7	13.5		13.9		13.7
<b>Recommended consumption of FVG</b>										
Yes	47.2	0.778	45.7	0.571	46.7	11.0	0.512	10.5	0.398	10.8
No	48.8		40.8		45.5	13.3		14.8		13.9
<b>Regular consumption of beans</b>										
Yes	47.4	0.527	41.2	0.572	44.6	10.6	0.049	13.9	0.880	12.1
No	50.9		46.4		49.7	18.0		12.9		16.7
<b>Meat with excessive fat</b>										
No	49.3	0.323	46.1	0.041	48.1	12.0	0.259	13.4	0.835	12.5
Yes	40.4		28.9		33.2	18.7		14.9		16.3
<b>Milk with full fat content</b>										
No	53.4	0.024	41.5	0.875	48.6	15.2	0.077	15.8	0.320	15.4
Yes	41.0		42.6		41.6	9.0		10.9		9.8
<b>Regular consumption of soda or artificial juice</b>										
No	48.6	0.746	43.7	0.183	46.7	12.5	0.609	14.4	0.452	13.2
Yes	44.9		27.5		34.5	17.0		9.0		12.2
<b>Regular consumption of sweets</b>										
No	47.9	0.568	43.5	0.099	46.1	13.6	0.087	14.5	0.209	14.0
Yes	51.9		26.5		43.5	6.3		6.5		6.4

Continue...

Table 1. Continuation.

Variables	Hypertension					Diabetes				
	Female sex		Male sex		Total	Female sex		Male sex		Total P
	P (%)*	P-value <sup>†</sup>	P (%)*	P-value <sup>†</sup>	P (%)*	P (%)*	P-value <sup>†</sup>	P (%)*	P-value <sup>†</sup>	(%)*
<b>Replacement of lunch or dinner with snack</b>										
No	49.9	0.083	42.9	0.284	45.3	1.6	0.032	14.4	0.163	13.9
Yes	61.3		29.1		51.0	4.7		5.9		5.1
<b>High salt consumption</b>										
No	47.6	0.113	42.7	0.571	45.7	12.7	0.916	14.7	0.429	13.5
Yes	64.3		36.1		47.0	12.0		7.1		9.0
<b>Health indicators</b>										
<b>BMI – overweight</b>										
No	32.4	0.000	28.4	0.013	31.1	8.6	0.042	6.1	0.009	7.7
Yes	59.0		47.7		54.0	15.4		17.1		16.1
<b>Self-assessed poor/very poor health</b>										
No	47.0	0.039	39.2	0.000	43.8	12.7	0.887	12.9	0.125	12.8
Yes	69.8		89.6		77.1	11.8		28.7		18.0
<b>Self-reported dyslipidemia</b>										
No	38.2	0.000	36.1	0.017	37.3	48.9	0.092	13.2	0.702	11.6
Yes	63.8		55.0		60.8	51.1		15.2		15.8

Note: the results express the percentage for the population. \*Prevalence; <sup>†</sup>Statistical analysis performed was Pearson's chi-square test. BMI = body mass index; FVG = fruits, vegetables and greens.

**Table 2.** Prevalence and prevalence ratios (crude and adjusted) for prior medical diagnosis of hypertension reported by women (n = 566) and men (n = 300), according to sociodemographic, behavioral, food consumption and health indicator variables. João Pessoa, Paraíba, Brazil (2014)

Variables	Women		Men	
	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*
<b>Sociodemographic indicators</b>				
<b>Age group</b>				
45-54 years	1.0	1.0	1.0	1.0
55-64 years	1.2 (0.9-1.7) <sup>‡</sup>	1.1 (0.9-1.5)	1.5 (1.0-2.4) <sup>‡</sup>	1.3 (0.9-2.0)
≥ 65 years	1.4 (1.1-1.8) <sup>‡</sup>	1.3 (1.0-1.7) <sup>§</sup>	1.5 (1.0-2.3) <sup>‡</sup>	1.3 (0.9-1.9)
<b>Marital status</b>				
Single	1.0	-	1.0	-
Married/stable partnership	1.2 (0.8-1.8)	-	1.1 (0.5-2.2)	-
Widowed	1.2 (0.8-1.8)	-	1.3 (0.5-3.3)	-
Separated/divorced	1.4 (0.9-2.2)	-	1.0 (0.4-2.7)	-
<b>Education</b>				
≥ 12 years	1.0	-	1.0	-
9-11 years	1.0 (0.8-1.4)	-	1.3 (0.8-1.9)	-
5-8 years	1.1 (0.8-1.5)	-	1.0 (0.6-1.7)	-
0-4 years	1.3 (0.9-1.7)	-	1.2 (0.8-2.0)	-
<b>Possession of health insurance</b>				
Yes	1.0	-	1.0	1
No	1.1 (0.8-1.3)	-	0.7 (0.5-1.0) <sup>‡</sup>	0.8 (0.6-1.1)
<b>Behavioral indicators</b>				
<b>Smokers</b>				
No	1.0	1.0	1.0	-
Yes	0.6 (0.3-1.1) <sup>‡</sup>	0.6 (0.4-1.1)	0.9 (0.6-1.6)	-
<b>Former smokers</b>				
No	1.0	-	1.0	-
Yes	0.9 (0.7-1.2)	-	0.9 (0.6-1.3)	-

Continue...

Table 2. Continuation.

Variables	Women		Men	
	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*
<b>Physically inactive</b>				
No	1.0	1.0	1.0	1.0
Yes	1.1 (0.9-1.5) <sup>‡</sup>	0.9 (0.7-1.2)	1.3 (0.9-1.9) <sup>‡</sup>	1.1 (0.8-1.6)
<b>Food consumption indicators</b>				
<b>Regular consumption of FVG</b>				
Yes	1.0	-	1.0	-
No	1.1 (0.9-1.4)	-	0.9 (0.6-1.3)	-
<b>Recommended consumption of FVG</b>				
Yes	1.0	-	1.0	-
No	1.0 (0.8-1.3)	-	0.8 (0.6-1.3)	-
<b>Regular consumption of beans</b>				
Yes	1.0	-	1.0	-
No	1.0 (0.8-1.3)	-	1.1 (0.7-1.6)	-
<b>Meats with excessive fat</b>				
No	1.0	-	1.0	1.0
Yes	0.8 (0.5-1.2)	-	0.6 (0.3-1.0) <sup>‡</sup>	0.7 (0.4-1.2)
<b>Milk with full fat content</b>				
No	1.0	1.0	1.0	-
Yes	0.7 (0.6-0.9) <sup>‡</sup>	0.7 (0.6-0.9) <sup>§</sup>	1.0 (0.7-1.4)	-
<b>Regular consumption of soda or artificial juice</b>				
No	1.0	-	1.0	1.0
Yes	0.9 (0.5-1.5)	-	0.6 (0.2-1.3)	0.7 (0.4-1.4)
<b>Regular consumption of sweets</b>				
No	1.0	-	1.0	1.0
Yes	1.0 (0.8-1.4)	-	0.6 (0.3-1.1) <sup>‡</sup>	0.7 (0.3-1.3)
<b>Replacement of lunch or dinner with snack</b>				
No	1.0	1.0	1.0	-
Yes	1.3 (0.9-1.7) <sup>‡</sup>	1.2 (0.9-1.5)	0.6 (0.3-1.4)	-
<b>High salt intake</b>				
No	1.0	1.0	1.0	-
Yes	1.3 (0.9-1.8) <sup>‡</sup>	1.2 (0.9-1.7)	0.8 (0.4-1.5)	-
<b>Health indicators</b>				
<b>BMI – overweight</b>				
No	1.0	1.0	1.0	1.0
Yes	1.8 (1.4-2.3) <sup>‡</sup>	1.7 (1.3-2.2) <sup>§</sup>	1.6 (1.0-2.6) <sup>‡</sup>	1.7 (1.1-2.5) <sup>§</sup>
<b>Self-assessed poor/very poor health</b>				
No	1.0	1.0	1.0	1.0
Yes	1.4 (1.1-2.0) <sup>‡</sup>	1.3 (1.0-1.8) <sup>§</sup>	2.2 (1.7-2.9) <sup>‡</sup>	1.9 (1.4-2.5) <sup>§</sup>
<b>Dyslipidemia</b>				
No	1.0	1.0	1.0	1.0
Yes	1.6 (1.3-2.0) <sup>‡</sup>	1.5 (1.2-1.8) <sup>§</sup>	1.5 (1.0-2.1) <sup>‡</sup>	1.2 (0.9-1.7)

\*PR = prevalence ratio; CI = confidence interval; <sup>†</sup>Statistical analysis adjusted using Poisson regression, performed only on independent variables that presented significance  $\leq 0.20$  ( $P \leq 0.20$ ) in Pearson's chi-square test; <sup>‡</sup> $P \leq 0.20$ ; <sup>§</sup> $P \leq 0.05$ . BMI = body mass index; FVG = fruits, vegetables and greens.

milk remained associated with lower prevalence of hypertension in women. In the adjusted analysis for men, overweight and self-rated poor health were independently associated with hypertension. The results differed between the age groups of 55-64 years and  $\geq 65$  years. Presence of a previous medical diagnosis of dyslipidemia lost its statistical significance in the adjusted analysis.

Table 3 shows the crude and adjusted analyses on factors associated with diabetes in women and men. In the adjusted analysis relating to women, the age group of 55-64 years, educational level of 0-4 years and not consuming beans regularly remained independently associated with higher prevalence of diabetes. This differed from the age group  $\geq 65$  years and educational attainment

**Table 3.** Prevalence and prevalence ratios (crude and adjusted) for prior medical diagnosis of diabetes reported by women (n = 566) and men (n = 297), according to sociodemographic, behavioral, food consumption and health indicator variables. João Pessoa, Paraíba, Brazil (2014)

Variables	Women		Men	
	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*
<b>Sociodemographic indicators</b>				
<b>Age group</b>				
45-54 years	1.0	1.0	1.0	1.0
55-64 years	2.5 (1.1-5.4) <sup>‡</sup>	2.0 (0.9-4.4) <sup>§</sup>	5.6 (2.1-14.8) <sup>‡</sup>	5.1 (1.9-13.4) <sup>§</sup>
≥ 65 years	2.5 (1.2-5.1) <sup>‡</sup>	1.8 (0.8-3.9)	4.2 (1.6-10.7) <sup>‡</sup>	4.0 (1.4-10.9) <sup>§</sup>
<b>Marital status</b>				
Single	1.0	-	1.0	1.0
Married/stable partnership	1.3 (0.5-3.1)	-	27.8 (3.5-216.9) <sup>‡</sup>	17.7 (2.0-153.0) <sup>§</sup>
Widowed	1.9 (0.8-4.7)	-	7.4 (0.6-91.4) <sup>‡</sup>	3.7 (0.2-54.9)
Separated/divorced	1.6 (0.5-5.3)	-	6.1 (0.4-77.2) <sup>‡</sup>	6.5 (0.4-97.3)
<b>Education</b>				
≥ 12 years	1.0	1.0	1.0	-
9-11 years	1.7 (0.7-4.0)	1.7 (0.7-4.1)	0.8 (0.4-1.8)	-
5-8 years	2.4 (0.9-5.8)	2.0 (0.8-5.0)	0.7 (0.2-2.1)	-
0-4 years	3.3 (1.4-7.7) <sup>‡</sup>	2.5 (1.0-6.3) <sup>§</sup>	1.0 (1.4-2.5)	-
<b>Possession of health insurance</b>				
Yes	1.0	-	1.0	-
No	1.3 (0.7-2.3)	-	0.7 (0.3-1.4)	-
<b>Behavioral indicators</b>				
<b>Smokers</b>				
No	1.0	-	1.0	-
Yes	1.4 (0.5-3.7)	-	1.2 (0.4-3.1)	-
<b>Former smokers</b>				
No	1.0	1.0	1.0	1.0
Yes	0.6 (0.3-1.2) <sup>‡</sup>	0.7 (0.3-1.4)	2.0 (1.0-4.2) <sup>‡</sup>	1.6 (0.8-3.2)
<b>Physically inactive</b>				
No	1.0	1.0	1.0	-
Yes	1.5 (0.8-2.6)	1.0 (0.6-1.7)	1.0 (0.4-2.2)	-
<b>Food consumption indicators</b>				
<b>Regular consumption of FVG</b>				
Yes	1.0	-	1.0	-
No	1.1 (0.6-1.9)	-	1.0 (0.4-2.1)	-
<b>Recommended consumption of FVG</b>				
Yes	1.0	-	1.0	-
No	1.2 (0.6-2.1)	-	1.4 (0.6-3.1)	-
<b>Regular consumption of beans</b>				
Yes	1.0	1.0	1.0	-
No	1.6 (1.0-2.8) <sup>‡</sup>	1.6 (1.0-2.7) <sup>§</sup>	0.9 (0.3-2.5)	-
<b>Meats with excessive fat</b>				
No	1.0	-	1.0	-
Yes	1.5 (0.7-3.2)	-	1.1 (0.4-2.8)	-
<b>Milk with full fat content</b>				
No	1.0	1.0	1.0	-
Yes	0.5 (0.3-1.0) <sup>‡</sup>	0.6 (0.3-1.1)	0.6 (0.3-1.4)	-
<b>Regular consumption of soda or artificial juice</b>				
No	1.0	-	1.0	-
Yes	1.3 (0.4-4.4)	-	0.6 (0.1-2.2)	-

Continue...

Table 3. Continuation.

Variables	Women		Men	
	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*	Crude PR* 95% CI*	Adjusted <sup>†</sup> PR* 95% CI*
<b>Regular consumption of sweets</b>				
No	1.0	1.0	1.0	1.0
Yes	0.4 (0.1-1.1) <sup>‡</sup>	0.5 (0.1-1.3)	0.4 (0.1-1.7) <sup>‡</sup>	0.5 (0.1-2.1)
<b>Replacement of lunch or dinner with snack</b>				
No	1.0	1.0	1.0	1.0
Yes	0.3 (0.1-0.9) <sup>‡</sup>	0.3 (0.1-1.0) <sup>§</sup>	0.4 (0.1-1.5) <sup>‡</sup>	0.6 (0.1-2.6)
<b>High salt intake</b>				
No	1.0	-	1.0	-
Yes	0.9 (0.3-2.7)	-	0.4 (0.7-3.2)	-
<b>Health indicators</b>				
<b>BMI – overweight</b>				
No	1.0	1.0	1.0	1.0
Yes	1.7 (1.0-3.1) <sup>‡</sup>	1.7 (0.9-3.0)	2.8 (1.2-6.3) <sup>‡</sup>	2.2 (0.9-4.9)
<b>Self-assessed poor/very poor health</b>				
No	1.0	-	1.0	1.0
Yes	0.9 (0.3-2.6)	-	2.2 (0.8-5.8) <sup>‡</sup>	1.8 (0.7-4.4)
<b>Dyslipidemia</b>				
No	1	1	1.0	-
Yes	1.5 (0.9-2.6) <sup>‡</sup>	1.3 (0.8-2.1)	1.1 (0.5-2.3)	-

\*PR = prevalence ratio; CI = confidence interval; <sup>†</sup>Statistical analysis adjusted using the Poisson regression, performed only on independent variables that presented significance  $\leq 0.20$  ( $P \leq 0.20$ ) in Pearson's chi-square test; <sup>‡</sup> $P \leq 0.20$ ; <sup>§</sup> $P \leq 0.05$ . BMI = body mass index; FVG = fruits, vegetables and greens.

of 5-8 years, which lost their association with the prevalence of diabetes in the adjusted analysis. Replacing meals with snacks remained associated with lower prevalence of diabetes in women. In the adjusted analysis for men, the age groups of 55-64 years and  $\geq 65$  years remained independently associated with diabetes, along with being married or in a stable partnership.

## DISCUSSION

The results from the present study identified factors associated with hypertension and diabetes in the study population. For women, hypertension remained associated with the age group  $\geq 65$  years old and with higher prevalence of overweight, self-rated poor/very poor health and dyslipidemia. For men, hypertension was associated with higher prevalence of overweight and self-rated poor/very poor health. Regarding diabetes, in women, the age group of 55-64 years, educational attainment of 0-4 years and regular non-consumption of beans were associated with higher prevalence of this chronic disease. In men, the age groups of 55-64 years and  $\geq 65$  years were associated with higher prevalence of diabetes, along with being married or in a stable partnership.

The prevalence of hypertension identified in the present study was greater than that found through the Vigitel survey in João Pessoa (the state capital of Paraíba) in the years 2012<sup>14</sup> and 2013,<sup>15</sup>

when the self-reported frequencies of a medical diagnosis of this chronic disease among adults aged  $\geq 18$  years were 25.7% and 24.4%, respectively. The prevalence of diabetes was similar to that found in a study conducted in Florianópolis,<sup>16</sup> Santa Catarina, Brazil, in which data on elderly people aged  $\geq 60$  years with self-reported diagnoses of diabetes were evaluated. Moreover, the prevalence of diabetes identified in the present study was also greater than that found through the Vigitel survey in João Pessoa in the years 2012<sup>14</sup> and 2013,<sup>15</sup> when the self-reported frequencies of a medical diagnosis of diabetes among adults were 5.9% and 6.5%, respectively.

In the present study, higher prevalences of hypertension and diabetes occurred with advancing age, in agreement with previous research. Higher prevalence of noncommunicable diseases with advancing age is an expected result because of the characteristics of these diseases and structural and physiological changes that occur in the body during aging.<sup>16,17</sup> However, it is worth mentioning that, regarding diabetes, there was a slight decrease in prevalence with advancing age. This inverse relationship was also found in the ISA-SP<sup>18</sup> project (Health Surveys in the State of São Paulo) and in the SABE<sup>19</sup> study (Health, well-being and aging). One possible explanation might relate to survival bias, given the greater mortality among diabetics with increasing age, due to the great number of complications resulting from this disease.<sup>4,18</sup>

Self-assessed poor/very poor health was associated with hypertension in both genders. The literature generally indicates that health evaluations are worse among women, since they are the individuals who access healthcare services the most. Thus, women have greater concern for and perception of their health. On the other hand, men tend to self-evaluate their health as poor only in the presence of some disease.<sup>16</sup> In a study carried out by Carvalho et al.,<sup>20</sup> the prevalence of self-assessed poor health was significantly higher among individuals with lower educational level, those with chronic disease (hypertension, diabetes or obesity) and women, both in northeastern Brazil and in Portugal.

The present study also showed that dyslipidemia was significantly associated with hypertension among women. There is evidence of a correlation between lipid profile and systemic arterial pressure, as observed in metabolic syndrome.<sup>21</sup> Regarding food consumption variables, despite the consensus in the literature that consumption of foods that are considered to be risk factors for non-communicable chronic diseases (such as high-fat foods) and replacement of meals by snacks (usually composed of snack foods and fast food) have direct relationships with occurrences of chronic diseases, the present study did not confirm these association. These results may have two explanations: the women involved might already have been undergoing treatment, with dietary reeducation to control hypertension and diabetes, thus forming a framework of reverse causality; or these women might also have distorted their reporting of some foods, if they already knew their beneficial or even harmful effects on health. Individuals with diagnoses of non-communicable chronic diseases are more likely to attend healthcare services, where they are advised to change their eating and healthcare behaviors. In such cases, the inverse association is a positive indicator.<sup>22,23</sup>

Starting with the 2013 Vigitel survey,<sup>24</sup> questions regarding replacement of meals by snacks were included. In João Pessoa, interviewees in this situation who had been replacing meals with regional foods such as tapioca, couscous and other items that do not fit the definition of dinner may have been included. The questionnaire only became more specific after Vigitel 2015, through inclusion of positive responses regarding consumption of pizzas, sandwiches and other processed snacks, thus excluding items that are common in some regions, such as couscous and *tacacá*, among others.

Not consuming beans regularly was associated with higher prevalence of diabetes among women. Beans are legumes that traditionally have formed part of the Brazilian diet and adequate consumption of beans has been strongly associated with protection against several diseases, since it is one of the foods with proportionally larger amounts of dietary fiber, compared with other foods and constitutes an important item within healthy food consumption.<sup>25</sup> Some Brazilian studies on populations in the northeastern

and southeastern regions have shown that bean consumption has beneficial effects at the population level, through providing protective effects against body weight gain.<sup>26</sup>

The present study also found an association between lower schooling level (0-4 years) and higher prevalence of diabetes among women. This was similar to the findings from a study carried out in the city of Viçosa, Minas Gerais,<sup>27</sup> in which higher schooling levels were inversely associated with occurrences of diabetes among 621 elderly individuals aged 60 years and over. Likewise, in a study carried out in the municipality of Triunfo,<sup>28</sup> in the backlands of the state of Pernambuco, Brazil, on a representative sample of 198 adults with a mean age of 57.7 years, all the cases of diabetes were among individuals who were illiterate or had only had elementary education. The fact that the higher the schooling level is, the lower the chances are that individuals will develop hypertension and/or diabetes, demonstrates that government investment in education is paramount. Low educational level can hinder access to healthcare information and limit understanding of the guidelines regarding prevention and/or treatment of diabetes.<sup>27</sup>

Regarding marital status, for men, being married or in a stable partnership showed a statistically significant association with occurrences of diabetes. This result was contrary to those of other studies, such as GAZEL,<sup>29</sup> in which reports of non-communicable chronic diseases were more frequent among individuals living alone. That association seemed to result from greater exposure to behavioral risk factors for chronic diseases among single individuals.

The results from the present study also demonstrated that overweight was a determinant strongly associated with occurrences of hypertension. Other studies on elderly individuals in the municipalities of Marques de Souza (Rio Grande do Sul)<sup>30</sup> and Bauru (São Paulo)<sup>17</sup> and from the Vigitel survey,<sup>31</sup> conducted in all Brazilian state capitals, showed that between 20% and 30% of the prevalence of hypertension could be explained by an association between overweight and increased risk of developing this disease.<sup>31</sup>

Some limitations of the present study need to be pointed out. One limitation to be highlighted relates specifically to the methodology used in the Vigitel system: only individuals living in households that have a landline can be interviewed, which gives rise to the possibility of calibration bias. However, weighting factors through which it is sought through post-stratification to estimate the prevalence taking into account differences in the demographic characteristics of the Vigitel sample in relation to those of the entire population are used. Furthermore, the high response rate achieved through Vigitel contributes to the quality of the data.

Another limitation relates to the use of self-reported data, which can be influenced by individuals' access to medical diagnoses and their understanding of their health condition. The potential for information bias, with overestimation of height and

underestimation of weight, cannot be discarded given that Vigitel provides self-reported and unmeasured weight and height. However, validation studies on some Vigitel indicators have been conducted in Brazil,<sup>32,33</sup> showing agreement between the information reported through Vigitel and the information from household surveys. Vigitel has the advantage of being a non-invasive method in which it is easy to obtain data, at low cost.

Since Vigitel has a cross-sectional methodological design, it is not possible to establish any temporal cause-and-effect relationship among the associations between outcomes and independent variables. Therefore, it cannot distinguish whether the factors associated with hypertension and diabetes are causes or consequences of illness. However, recognizing the risk factors associated with chronic diseases is essential for identifying groups with specific needs and for guiding public policies, through establishing appropriate monitoring of these risk factors.

A further limitation of the present study relates to its extraction of Vigitel data, in which data from only one Brazilian state capital were separated out. This potentially reduced the statistical power of the tests through decreasing the sample size.

Moreover, only adults aged 45 and over were included, thus hindering knowledge of the behavior of the population under 45 years old. Since hypertension and diabetes are chronic diseases, these factors may have changed over the course of life, thereby reducing the effect observed in this study. However, this is a limitation of the cross-sectional study design.

Despite the limitations identified, some potentialities of this study stood out. Cross-sectional population-based studies on representative samples conducted through telephone surveys are of great relevance because they are fast and cost-effective alternatives. They thus constitute an important epidemiological tool for determining the dimensions of problems, through estimating indicators for health conditions, health-related behaviors and access to and use of healthcare and disease treatment services. Such studies provide support for actions that may be implemented to promote health and prevent non-communicable chronic diseases in the reference population or in others with similar characteristics.

## CONCLUSION

The results obtained confirmed the importance of hypertension and diabetes as a public health problem and identified a list of factors associated with these chronic diseases, among which some would be susceptible to intervention. Thus, this study identified an urgent need for specific interventions in this population, with implementation of healthcare aimed towards minimizing the complications arising from these pathological conditions, as well as preventing the onset of other chronic diseases. These interventions should be conducted in such a way that they allow

individuals to discuss issues relating to their chronic conditions and the risk factors involved, while at the same time enabling stimulation and providing conditions that encourage these individuals to adopt healthier lifestyles.

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# Evaluation of waist-to-height ratio as a predictor of insulin resistance in non-diabetic obese individuals.

## A cross-sectional study

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### KEY WORDS:

Anthropometry.  
Obesity.  
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### ABSTRACT

**BACKGROUND:** Insulin resistance (IR) and progressive pancreatic  $\beta$ -cell dysfunction have been identified as the two fundamental features in the pathogenesis of obesity and non-insulin-dependent diabetes mellitus. We aimed to investigate correlations between anthropometric indices of obesity and IR in non-diabetic obese individuals, and the cutoff value from receiver operating characteristic (ROC) curve analysis.

**DESIGN AND SETTING:** Cross-sectional study conducted in a private clinic.

**METHODS:** We included obese individuals (body mass index, BMI  $\geq 30$  kg/m<sup>2</sup>) with no diabetes mellitus (fasting glucose levels  $\leq 126$  mg/dl). The participants were evaluated for the presence of cardiovascular risk factors and through anthropometric measurements and biochemical tests. Furthermore, IR was assessed indirectly using the homeostatic model assessment (HOMA)-IR and HOMA- $\beta$  indexes. The area under the curve (AUC) of the variables was compared. The sensitivity, specificity and cutoff of each variable for diagnosing IR were calculated.

**RESULTS:** The most promising anthropometric parameters for indicating IR in non-diabetic obese individuals were waist-to-height ratio (WHtR), waist circumference (WC) and BMI. WHtR proved to be an independent predictor of IR, with risk increased by 0.53% in HOMA-IR, 5.3% in HOMA- $\beta$  and 1.14% in insulin. For HOMA-IR, WHtR had the highest AUC value (0.98), followed by WC (0.93) and BMI (0.81). For HOMA- $\beta$ , WHtR also had the highest AUC value (0.83), followed by WC (0.75) and BMI (0.73). The optimal WHtR cutoff was 0.65 for HOMA-IR and 0.67 for HOMA- $\beta$ .

**CONCLUSION:** Among anthropometric obesity indicators, WHtR was most closely associated with occurrences of IR and predicted the onset of diabetes in obese individuals.

### INTRODUCTION

Insulin resistance (IR) is considered to be one of the main risk factors for cardiovascular disease (CVD). It is associated with several metabolic abnormalities such as impaired glucose tolerance, non-insulin-dependent diabetes mellitus (NIDDM), hypertension and dyslipidemia.<sup>1,2</sup> Maintenance of normal blood glucose comes mainly from the ability of  $\beta$ -pancreatic cells to secrete insulin and the sensitivity of the target tissues to respond to normal levels of insulin in the bloodstream.<sup>3</sup>

The homeostasis model assessment (HOMA) is a widely validated clinical and epidemiological tool for estimating IR and  $\beta$ -cell function. It is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin.<sup>4</sup> HOMA-IR and HOMA- $\beta$  have been adopted as an alternative to the gold standard method, i.e. the hyperinsulinemic-euglycemic clamp technique. Although use of HOMA indices requires an invasive access,<sup>5</sup> it is inexpensive and easy to apply.<sup>6</sup>

One aspect of research on obesity that is currently attracting attention is the distribution of fat in the body. Diabetes, atherosclerosis and sudden cardiac death occur quite frequently among obese people, but when obesity is centralized in the abdominal region, the negative repercussions (both metabolic and cardiovascular) are more significant.<sup>7</sup> Several studies have evaluated the correlation between IR and anthropometric indices of obesity such as body mass index (BMI), waist circumference (WC), neck circumference (NC) and hip circumference (HP). They have demonstrated that the distribution of visceral fat causes significant damage to the insulin-signaling pathway due to secretion of adipokines, e.g. C-reactive protein (CRP),<sup>2,8,9</sup> thus leading to increased cardiometabolic risk.<sup>10</sup> Therefore, obesity is the most prominent predictor of IR and diabetes.<sup>11</sup>

Anthropometry is considered to be a non-invasive tool for early diagnosis of the onset of NIDDM. In addition, it provides an alternative evaluation of IR at lower cost that is accessible for application in epidemiological studies and primary care within health services.<sup>8</sup> However, there is no consensus regarding which anthropometric measurement is most indicative of IR in non-diabetic obese subjects, or regarding the cutoff values.

## OBJECTIVE

We aimed to investigate the correlations between anthropometric indices of obesity and IR in non-diabetic obese individuals, and to identify the best cutoff values of these indices for predicting IR, through using receiver operating characteristic (ROC) curve analyses.

## METHODS

### Participants

This study used a cross-sectional design. The participants were selected as a convenience sample of consecutive patients admitted between 2013 and 2015, when they presented the following inclusion criteria: BMI  $\geq 30$  kg/m<sup>2</sup> and no diabetes mellitus (DM) (reported or fasting blood glucose  $\leq 126$  mg/dl).<sup>12,13</sup> We enrolled 136 obese individuals, comprising 72 men and 64 women, at the Obesity Clinic of the Angiocorpore Institute of Cardiovascular Medicine, located in the city of Santos, São Paulo, Brazil. They had been referred for the examinations because of a variety of medical indications. This study formed part of a larger study assessing the determinants of exercise intolerance among obese individuals. All the participants agreed to participate, and none of them presented abnormalities during the examinations that would exclude them.

The Ethics Committee for Research on Human Beings of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) approved this study under the number 1.079.239. Furthermore, an informed consent statement was signed by all of these volunteers.

### Anthropometric obesity indices

Body weight and height were measured by using a weighing scale with stadiometer that measured to precisions of the nearest 0.1 kg and 1 cm (Toledo, São Paulo, Brazil). The individuals were weighed without shoes. The neck (NC), waist (WC) and hip (HC) circumferences were measured in cm using an inelastic tape (Sanny) with precision of 1 mm. We measured NC at the midpoint of the neck; WC at the midpoint between the last rib and the iliac crest; and HC at the point of greatest gluteal protuberance.<sup>14,15</sup> From these anthropometric measurements, we obtained indices relating to cardiometabolic health:

waist-to-hip ratio (WHR), waist/height ratio (WHTR), body mass index (BMI =  $\text{weight}_{\text{kg}}/\text{height}_{\text{m}}^2$ ) and body shape index (BSI =  $\text{WC}/\text{BMI}^{2/3} \times \text{height}^{1/3}$ ).<sup>16</sup>

### Blood test

Blood samples were collected for laboratory-based biochemical measurements after the participants had fasted for 12 hours. We quantified C-reactive protein (CRP, ng/ml), total cholesterol (mg/dl), HDL cholesterol (mg/dl), LDL cholesterol (mg/dl), insulin (IU/dl) and glucose (mg/dl). Glucose values were converted from mg/dl to mmol/l using the conversion factor 0.555.<sup>13</sup>

### IR assessment

We used the homeostasis model assessments HOMA-IR and HOMA- $\beta$  to indirectly determine IR, based on glucose and insulin values proposed by Matthews et al.<sup>3</sup> IR was defined as situations with HOMA-IR  $\geq 2.7$ ,<sup>17-21</sup> and dysfunction of  $\beta$ -cells as situations with HOMA- $\beta > 175$ .<sup>4,22</sup>

### Cardiovascular risk assessment

We assessed self-reported cardiovascular risk factors in accordance with the recommendations of the American College of Sports Medicine (ACSM). The participants were asked to report any previous diagnosis of the main cardiovascular risk factors such as arterial hypertension, dyslipidemia and diabetes, along with their age, situation of physical inactivity and smoking status. We considered that the participants were physically inactive if they reported doing less than 150 minutes per week of moderate-to-vigorous physical activity.<sup>23</sup>

### Statistical analysis

We assessed correlations between anthropometric indices and HOMA-IR values, HOMA- $\beta$  values and insulin concentration using Pearson correlation coefficients. Three models of stepwise multiple linear regressions were then fitted, with HOMA-IR, HOMA- $\beta$  and insulin as the main outcomes. The main predictors that we chose were the anthropometric indices that significantly correlated with outcomes after univariate analysis. We checked for multicollinearity in the models by means of variation inflation factor (VIF) values  $< 4$ . The models were also adjusted for age, sex and cardiovascular risk factors.

We fitted ROC curves to assess the best cutoff points for anthropometric measurements for predicting clinically high values of HOMA-IR and HOMA- $\beta$  as surrogate measurements for IR. The areas under the ROC curves (AUC) and the 95% confidence intervals (95% CI) were used to compare the diagnostic value of various obesity indices. We considered that values above 0.80 were excellent. The main anthropometric indices selected after multiple linear regression were used to obtain the optimal cutoff

point for diagnosing IR. We calculated the sensitivity, specificity, positive and negative likelihood ratios and Youden index in relation to these values.

All tests were evaluated at a two-tailed alpha level of 0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23 (SPSS Inc., Chicago, USA), and the MedCalc package, version 17 (MedCalc Software bvba, Belgium).

## RESULTS

### Baseline characteristics of the participants

The men and women involved in the present study were on average middle-aged. We found significantly higher values for weight, height, WC, WHR, NC and BSI among the men, while HC and BMI were significantly higher among the women. The participants were mostly physically inactive. We observed a greater proportion of dyslipidemia among the men and higher fasting glucose among the women (Table 1).

When stratified according to nutritional status, we found progressively impaired values for fasting insulin, HOMA-IR and HOMA- $\beta$  with increasing severity of obesity, while CRP presented

a significant difference only at obesity level I and total cholesterol at obesity level III (Table 2).

### Correlation and multiple regression analysis

We found strong correlations of WHtR, WC and BMI with HOMA-IR, HOMA- $\beta$  and fasting insulin. On the other hand, WHR, NC and BSI showed weak correlations (Table 3). A step-wise multiple linear regression analysis was performed with HOMA-IR, HOMA- $\beta$  and insulin as dependent variables. After adjustment for age, sex and obesity indices, WHtR proved to be an independent predictor of IR in this study (Table 4).

### ROC curves

The abilities of WHtR, WC and BMI to detect IR were compared using ROC curves. For HOMA-IR, we found an AUC of 0.98 for WHtR, 0.83 for WC and 0.81 for BMI, such that the AUC was significantly greater for WHtR than for WC (difference between areas = 0.150;  $P < 0.001$ ) and BMI (difference between areas = 0.171;  $P < 0.001$ ). We found that there was no significant difference in AUC between WC and BMI (difference between areas = 0.021;  $P = 0.629$ ) (Figure 1). Regarding HOMA- $\beta$ , the AUC of 0.83 for WHtR

**Table 1.** General characteristics of the study sample according to sex. Mean  $\pm$  standard deviation (SD).

	Females (n = 64)	Males (n = 72)	P
Age (years)	37 $\pm$ 10	34 $\pm$ 8	0.054
Weight (kg)	106 $\pm$ 11	120 $\pm$ 17*	0.000
Height (m)	1.62 $\pm$ 0.05	1.75 $\pm$ 0.08*	0.000
Body mass index (kg/m <sup>2</sup> )	40.5 $\pm$ 4.8	38.8 $\pm$ 4.5*	0.034
Waist circumference (cm)	111 $\pm$ 8	118 $\pm$ 11*	0.000
Hip circumference (cm)	129 $\pm$ 9	120 $\pm$ 9*	0.000
Waist-to-hip ratio	0.86 $\pm$ 0.07	0.98 $\pm$ 0.07*	0.000
Neck circumference (cm)	38 $\pm$ 3	44 $\pm$ 3*	0.000
Body shape index	7.4 $\pm$ 0.4	7.8 $\pm$ 0.45*	0.000
Waist-to-height ratio	0.69 $\pm$ 0.06	0.68 $\pm$ 0.06	0.333
<b>Cardiovascular risk assessment and biochemical analysis</b>			
Arterial hypertension	20 (23.8)	15 (20.0)	0.592
Dyslipidemia	10 (11.9)	21 (28.0)*	0.020
Physical inactivity	63 (75.0)	55 (73.3)	0.821
Current smoking	13 (15.4)	14 (18.6)	0.620
HDL (mg/dl)	50 $\pm$ 15	50 $\pm$ 13	1.000
LDL (mg/dl)	115 $\pm$ 32	121 $\pm$ 34	0.292
Total cholesterol (mg/dl)	196 $\pm$ 38	201 $\pm$ 32	0.406
Fasting glucose (mg/dl)	93 $\pm$ 10	89 $\pm$ 11*	0.028
Fasting insulin (IU/ml)	19 $\pm$ 9	17 $\pm$ 10	0.224
HOMA-IR	4.72 $\pm$ 2.58	3.81 $\pm$ 2.50	0.058
HOMA- $\beta$	71.6 $\pm$ 35.8	64.9 $\pm$ 42.9	0.327

HDL = high-density lipoprotein; LDL = low-density lipoprotein; HOMA-IR = homeostasis model assessment - insulin resistance; HOMA- $\beta$  = homeostasis model assessment - beta-cell function.

\* $P < 0.05$  = females versus males.

**Table 2.** Description of anthropometric measurements and biochemical analysis between obesity levels. Mean  $\pm$  standard deviation (SD).

	Obesity I (n = 20)	Obesity II (n = 63)	Obesity III (n = 53)
<b>Anthropometric parameters</b>			
Weight (kg)	101 $\pm$ 10.5	108 $\pm$ 12.0	124 $\pm$ 15.6 <sup>d</sup>
Height (cm)	172 $\pm$ 0.0	169 $\pm$ 0.0	166 $\pm$ 0.0 <sup>b</sup>
Waist circumference (cm)	107 $\pm$ 6	113 $\pm$ 8	121 $\pm$ 10 <sup>d</sup>
Hip circumference (cm)	115 $\pm$ 4.6	121 $\pm$ 7.2	133 $\pm$ 8.8 <sup>ad</sup>
Neck circumference (cm)	40 $\pm$ 3.1	41 $\pm$ 4.2	41 $\pm$ 4.8
Waist-to-hip ratio	0.93 $\pm$ 0.07	0.93 $\pm$ 0.89	0.90 $\pm$ 0.10
Waist-to-height ratio	0.62 $\pm$ 0.03	0.67 $\pm$ 0.05	0.73 $\pm$ 0.06 <sup>ad</sup>
Body mass index (kg/m <sup>2</sup> )	33.8 $\pm$ 0.8	37.6 $\pm$ 1.3	44.9 $\pm$ 3.6 <sup>ad</sup>
Body shape index	7.8 $\pm$ 0.4	7.7 $\pm$ 0.5	7.4 $\pm$ 0.5 <sup>bc</sup>
<b>Biochemical analysis</b>			
C-reactive protein (ng/ml)	2.15 $\pm$ 2.86	0.93 $\pm$ 1.15	0.92 $\pm$ 0.98 <sup>e</sup>
Total cholesterol (mg/dl)	198 $\pm$ 35	191 $\pm$ 32	208 $\pm$ 38 <sup>c</sup>
HDL (mg/dl)	53 $\pm$ 16	48 $\pm$ 13	51 $\pm$ 14
LDL (mg/dl)	124 $\pm$ 25	116 $\pm$ 27	119 $\pm$ 43
Fasting glucose (mg/dl)	88 $\pm$ 9	91 $\pm$ 11	93 $\pm$ 11
Fasting insulin (IU/ml)	9.6 $\pm$ 4.0	15.0 $\pm$ 6.2	25.6 $\pm$ 11.6 <sup>d</sup>
HOMA-IR	2.1 $\pm$ 1.0	3.4 $\pm$ 1.6	6.0 $\pm$ 2.8 <sup>d</sup>
HOMA- $\beta$	35.5 $\pm$ 15	55.7 $\pm$ 23	95.3 $\pm$ 45 <sup>d</sup>

HDL = high-density lipoprotein; LDL = low-density lipoprotein; HOMA-IR = homeostasis model assessment - insulin resistance; HOMA- $\beta$  = homeostasis model assessment - beta-cell function.

a = obesity I versus obesity II,  $P < 0.05$ . b = obesity I versus obesity III,  $P < 0.05$ .

c = obesity II versus obesity III,  $P < 0.05$ . d = obesity I and obesity II versus obesity III,  $P < 0.05$ . e = obesity II and obesity III versus obesity I,  $P < 0.05$ .

was significantly greater than the AUC for WC (0.75, difference between areas = 0.082; P = 0.013) and BMI (0.73, difference between areas = 0.099; P = 0.009), with no significant difference between WC and BMI (difference between areas = 0.017; P = 0.727) (Figure 2). The best cutoff points for HOMA-IR were 0.65, 113 cm and 38.76 kg/m<sup>2</sup> and for HOMA-β were 0.67, 112 cm and 37.61 kg/m<sup>2</sup>, respectively for WHtR, WC and BMI (Table 5).

**DISCUSSION**

In the present study, we observed that not all the anthropometric parameters studied were significantly associated with HOMA-IR

and HOMA-β. The most promising anthropometric parameters for indicating IR in non-diabetic obese adults were WHtR, WC and BMI. Our results suggest that there are advantages to using WHtR. In our analysis, we observed that the risk of IR was raised by 0.53% in HOMA-IR, 5.3% in HOMA-β and 1.14% in insulin for each additional 1% increase in WHtR (= 0.01). Thus, WHtR was a predictor for the degree of IR and predisposition towards diabetes in our sample of obese individuals. Recently, Vikam et al.<sup>10</sup> observed increased odds ratios for hyperinsulinemia and metabolic syndrome among individuals with WHtR > 0.5.

Use of WHtR for detecting abdominal obesity and its associated risks to health was first proposed in the 1990s.<sup>24</sup> The growing

**Table 3.** Matrix of correlations between obesity indices and values for homeostasis model assessment - insulin resistance (HOMA-IR) and for HOMA - beta-cell function (HOMA-β) in the study sample

		HOMA-IR	HOMA-β	Insulin (IU/ml)	WHtR	WC (cm)	BMI (kg/m <sup>2</sup> )	WHR	NC (cm)	BSI
HOMA-IR	r	1	0.853*	0.920*	0.846*	0.648*	0.669*	0.164	0.114	0.197 <sup>†</sup>
	p		0.00	0.00	0.00	0.00	0.00	0.061	0.197	0.024
	p <sup>†</sup>		0.086	0.334	0.242	0.974	0.399	0.377	0.377	0.019
HOMA-β	r	0.753*	1	0.944*	0.905*	0.753*	0.690*	0.277*	0.192 <sup>†</sup>	0.283*
	p	0.00		0.00	0.00	0.00	0.00	0.001	0.029	0.001
	p <sup>†</sup>	0.086		0.097	0.163	0.764	0.154	0.635	0.023	0.078
Insulin	r	0.920*	0.944*	1	0.935*	0.754*	0.720*	0.243*	0.163	0.267*
	p	0.00	0.00		0.00	0.00	0.00	0.005	0.064	0.002
	p <sup>†</sup>	0.334	0.097		0.186	0.239	0.644	0.512	0.096	0.086
WHtR	r	0.846*	0.905*	0.935*	1	0.876*	0.811*	0.452*	0.314*	0.448*
	p	0.00	0.00	0.00		0.00	0.00	0.00	0.00	0.00
	p <sup>†</sup>	0.242	0.163	0.186		0.533	0.155	0.088	0.274	0.085
WC (cm)	r	0.648*	0.753*	0.754*	0.876*	1	0.688*	0.658*	0.604*	0.608*
	p	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00
	p <sup>†</sup>	0.974	0.764	0.239	0.533		0.256		0.422	0.168
BMI (kg/m <sup>2</sup> )	r	0.669*	0.690*	0.720*	0.811*	0.688*	1	0.051	0.222*	-0.106
	p	0.00	0.00	0.00	0.00	0.00		0.525	0.005	0.184
	p <sup>†</sup>	0.399	0.154	0.644	0.155	0.256		0.067	0.278	0.205
WHR	r	0.164	0.277*	0.243*	0.452*	0.658*	0.051	1	0.609*	0.832*
	p	0.061	0.001	0.005	0.00	0.00	0.525		0.00	0.00
	p <sup>†</sup>	0.377	0.635	0.512	0.088	0.533	0.067		0.533	0.090
NC (cm)	r	0.114	0.192 <sup>†</sup>	0.163	0.314*	0.604*	0.222*	0.609*	1	0.444*
	p	0.197	0.029	0.064	0.00	0.00	0.005	0.00		0.00
	p <sup>†</sup>	0.377	0.023	0.064	0.274	0.422	0.278	0.533		0.067
BSI	r	0.197 <sup>†</sup>	0.283*	0.267*	0.448*	0.608*	-0.106	0.832*	0.444*	1
	p	0.024	0.001	0.002	0.00	0.00	0.184	0.00	0.00	
	p <sup>†</sup>	0.019	0.078	0.086	0.085	0.168	0.205	0.090	0.067	

r = Pearson coefficient; WHtR = waist-to-height ratio; WC = waist circumference; BMI = body mass index; WHR = waist-to-hip ratio; NC = neck circumference; BSI = body shape index. \*Significant correlations for all subjects; <sup>†</sup>Significant correlations for females versus males.

**Table 4.** Multiple regression analysis on obesity indices that predict insulin resistance

Dependent variable	Predictors	β	95% CI	R <sup>2</sup>	P
HOMA-IR	waist-to-height ratio	0.53*	0.47-0.59	0.71	< 0.01
HOMA-β	waist-to-height ratio	5.30*	4.93-5.67	0.82	< 0.01
Insulin (IU/ml)	waist-to-height ratio	1.14*	1.04-1.25	0.73	< 0.01

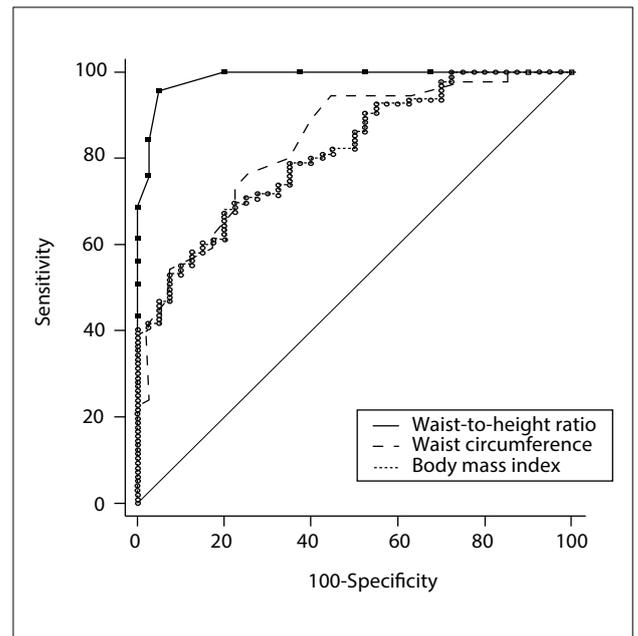
WHtR = waist-to-height ratio; HOMA-IR = homeostasis model assessment - insulin resistance; HOMA-β = homeostasis model assessment - beta-cell function. \*WHtR values are expressed in percentage. Models adjusted for age, sex, weight, waist circumference, neck circumference, body mass index, waist-hip ratio, waist-to-height ratio and body shape index.

body of literature showed that this abdominal obesity indicator could predict the cardiometabolic risk even better than BMI and WC.<sup>25</sup> A recent meta-analysis on studies evaluating different indices of adiposity showed that WHtR was a better predictor for hyperinsulinemia, diabetes, arterial hypertension, dyslipidemia, metabolic syndrome and other cardiovascular health problems than were BMI or WC, in both men and women.<sup>26</sup> In addition, our AUC values for this anthropometric obesity indicator were higher than in previous prediction studies with WHtR,<sup>11,27,28</sup> thus emphasizing the accuracy of AUC measurements for identifying IR in obese populations. According to Behboudi-Gandevani et al.,<sup>11</sup> WHtR may be proposed as a sensitive, inexpensive, noninvasive, simple-to-assess and easy-to-calculate tool for screening for IR.

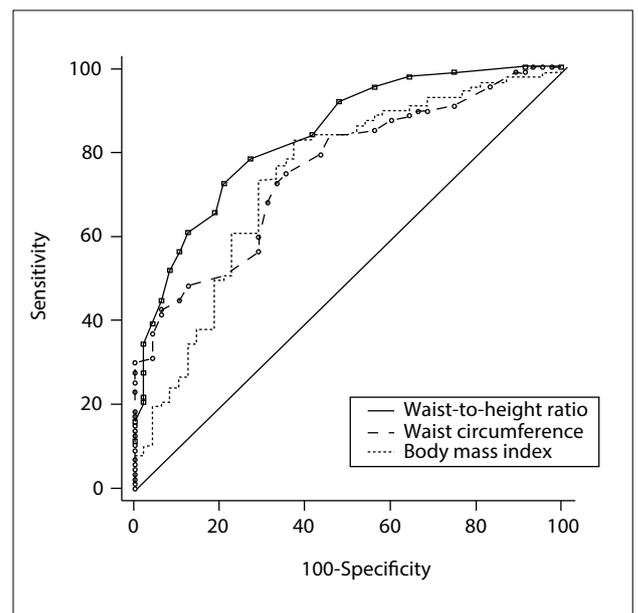
Taking into account that ethnicity and gender may influence body composition, studies on Brazilian and Indian overweight women also showed that the WHtR was the most important predictive measurement for IR and diabetes.<sup>27,29</sup> However, studies on men of different ethnicity indicated that BMI was the best predictor for IR.<sup>28,30,31</sup> It should be noted that BMI is characterized as an indicator of general adiposity because of its inability to assess the distribution of body fat, thus presenting a weaker relationship with visceral fat.<sup>27</sup> In a recent meta-analysis, Savva et al.<sup>32</sup> compared the association of BMI and WHtR with the cardiometabolic risk factor of diabetes in Asian and non-Asian populations. The data from cross-sectional studies indicated that WHtR is superior to BMI for detecting diabetes in both Asian and non-Asian populations. There are still few studies of this design on Brazilian populations, especially in relation to obese individuals.<sup>32</sup>

The risk of developing obesity-related comorbidities is proportional to the degree of obesity and, more specifically, the accumulation of visceral fat.<sup>33</sup> However, the presence of metabolic disorders varies considerably among obese individuals,<sup>34</sup> since it is known that there is one subgroup of obese individuals that seems to be protected against or is more resistant to developing cardiometabolic complications.<sup>35</sup> Nevertheless, regarding phenotypes for metabolic status and diabetes, healthy obese and metabolically unhealthy normal-weight individuals appear to have an equivalent risk.<sup>36</sup>

In the general population, a WHtR cutoff < 0.5 is recommended, which can be presented as a simple public health message that individuals should seek to maintain their WC as less than half of their height. We showed that the higher this ratio is, the higher the risk of indirect IR is, and we proposed a cutoff > 0.65 to identify IR in non-diabetic obese individuals. This indicates that there is a need for a specific evaluation on this population, for early detection of IR that could ultimately reduce the incidence or severity of diabetes and cardiovascular diseases.



**Figure 1.** Receiver operating characteristic (ROC) curve for anthropometric parameters that predict insulin resistance according to the homeostatic model assessment-insulin resistance (HOMA-IR). The areas under the ROC curves and the 95% confidence intervals (95% CI) were 0.98 (0.95-0.99) for waist-to-height ratio (WHtR); 0.93 (0.76-0.89) for waist circumference (WC); and 0.81 (0.74-0.87) for body mass index (BMI).



**Figure 2.** Receiver operating characteristic (ROC) curve for anthropometric parameters that predict insulin resistance according to the homeostatic model assessment (HOMA)- $\beta$ . The areas under the ROC curves and the 95% confidence intervals (95% CI) were 0.83 (0.76-0.89) for waist-to-height ratio (WHtR); 0.75 (0.67-0.82) for waist circumference (WC); and 0.73 (0.65-0.81) for body mass index (BMI).

**Table 5.** Optimal cutoff point values and their related sensitivity, specificity, positive and negative likelihood ratios and Youden index for obesity indices, regarding discrimination of insulin resistance

Outcome	Variable	Cutoff point	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	Youden index
HOMA-IR	Waist-to-height ratio	> 0.65	95.83 (89.7-98.9)	95.00 (83.1-99.4)	19.17 (5.0-74.0)	0.04 (0.02-0.1)	0.90
	Waist circumference (cm)	> 113.00	73.96 (64.0-82.4)	77.50 (61.5-89.2)	3.29 (1.8-5.9)	0.34 (0.2-0.5)	0.51
	Body mass index (kg/m <sup>2</sup> )	> 38.76	67.71 (57.4-76.9)	80.00 (64.4-90.9)	3.39 (1.8-6.4)	0.40 (0.3-0.6)	0.47
HOMA-β	Waist-to-height ratio	> 0.67	72.41 (61.8-81.5)	79.17 (65.0-89.5)	3.48 (2.0-6.1)	0.35 (0.2-0.5)	0.51
	Waist circumference (cm)	> 112.0	74.71 (64.3-83.4)	64.58 (49.5-77.8)	2.11 (1.4-3.2)	0.39 (0.3-0.6)	0.39
	Body mass index (kg/m <sup>2</sup> )	> 37.61	82.76 (73.2-90.0)	62.50 (47.4-76.0)	2.21 (1.5-3.2)	0.28 (0.2-0.5)	0.45

HOMA-IR = homeostasis model assessment - insulin resistance; HOMA-β = homeostasis model assessment - beta-cell function; +LR = positive likelihood ratio; -LR = negative likelihood ratio.

In summary, we found that WHtR may be useful in clinical practice due to its advantageous simplicity. Also, it is easy to calculate, does not require any special equipment other than an inelastic tape, and only requires some rater training.

The present study has limitations that should be considered. Our sample was not enough to extract the cutoff points according to sex. Since not all obese individuals have metabolic alterations, our strategy was to ascertain which anthropometric measurements were better correlated with IR, and whether non-diabetic obese individuals would present a cutoff point different from general population for predicting the onset of diabetes, thereby suggesting different reference values for a more accurate assessment in this specific group. Perhaps inclusion of a eutrophic group would have contributed towards reinforcing our important findings. Future research should aim to screen Brazilian obese populations, in order to provide support for our remarks.

## CONCLUSION

We can conclude that the WHtR is a strong predictor of IR, as assessed using HOMA, among non-diabetic obese adults. Our results suggest that WHtR can form a simple and powerful tool for screening for IR among these patients, since we found convincing AUC and sensitivity and specificity values for this index in detecting clinically high values of HOMA-IR and HOMA-β.

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# Temperament and character traits in major depressive disorder: a case control study

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## KEY WORDS:

Depressive disorder, major.  
Personality.  
Personality tests.

## ABSTRACT

**BACKGROUND:** Patients with major depressive disorder (MDD) have distinct personality traits, compared with control subjects, although the role of anxiety and positive and negative affects in this finding is unclear.

**DESIGN AND SETTING:** A case-control study enrolling 103 antidepressant-free depressed patients and 103 age and gender-matched controls was conducted at the University Hospital, University of São Paulo.

**METHODS:** The self-reported scales of the Positive and Negative Affect Schedule (PANAS), State-Trait Anxiety Inventory (STAI) and Cloninger's Temperament and Character Inventory (TCI) were applied. Temperament and character traits were compared between groups using multivariate and bivariate analyses of variance (MANOVA and ANOVA). The influence of anxiety and affect was further investigated using ANOVA and mediation analyses.

**RESULTS:** Depressed patients presented higher harm avoidance and lower self-directedness scores than controls. After adjustment for anxiety trait, harm avoidance was no longer significantly different between groups. Mediation analysis revealed that the anxiety trait, but not state-anxiety or affect, fully mediated the influence of group (depressed versus control subjects) on harm avoidance.

**CONCLUSIONS:** Our findings confirm that depressed patients present personality traits distinct from those of controls and suggest that MDD is not directly associated with harm avoidance, but that this effect is fully mediated through the anxiety trait.

## INTRODUCTION

Personality can be described as a dynamic form of organization, involving cognition, emotion, mood, impulsivity and social interactions, that modulates one's interaction with the environment.<sup>1</sup> Several models are used to study personality, from classic psychopathology and clinical psychiatry to more novel psychobiological approaches, such as the Cloninger temperament and character theory.<sup>2</sup>

According to Cloninger, temperament is responsible for automatic and emotional responses to environmental stimuli and encompasses four dimensions: novelty seeking (NS), consisting of behavioral activation to novel stimuli, exploratory activity, impulsivity, extravagance and disorderliness; harm avoidance (HA), a tendency towards inhibition or cessation of behaviors and avoidance of punishment and novelty; reward dependence (RD), a tendency to respond to reward and to learn to maintain rewarded behavior; and persistence (P), associated with perseverance, perfectionism, ambitiousness and eagerness of effort.

In contrast, character develops across the lifespan and is influenced by social and cultural experiences. Three dimensions are distinguished: self-directedness (SD), the ability to control and regulate behavior according to chosen goals; cooperativeness (C), associated with social acceptance and empathy; and self-transcendence (ST), associated with spirituality, altruism and identification with others.

Psychobiological models have been used in relation to several psychiatric disorders, including major depressive disorder (MDD). A recent meta-analysis<sup>3</sup> showed that depressed patients present higher HA and lower SD than controls. Nonetheless, this analysis also revealed that

the studies included presented low quality. For instance, several of them did not use a diagnostic interview scale, which is necessary for excluding other axis I disorders that also present altered temperament traits.<sup>4</sup> Moreover, most studies enrolled patients on antidepressant treatment, which can change temperament and character inventory (TCI) scores.<sup>5</sup> Furthermore, there are few studies on Brazilian populations and no study in Brazil has evaluated depressed patients using the TCI, which is important given that sociocultural factors influence character traits. Finally, most studies have not controlled for comparisons of TCI dimensions between depressed and control subjects according to anxiety and affect, which are associated with HA<sup>6</sup> and character traits,<sup>7</sup> respectively.

## OBJECTIVE

To fill these gaps, we aimed to compare the temperament and character traits of depressed patients with those of control subjects, in a Brazilian sample. We also explored the influence of anxiety and affect on personality traits and, particularly, on harm avoidance, which has been reported to be consistently altered in situations of depression.<sup>3</sup>

## METHODS

### Design

This was a case-control study in which data from depressed patients and control subjects were collected in a convenience sample. Participants were recruited between October 2013 and June 2015, at the University Hospital of the University of São Paulo, São Paulo, Brazil. Patients with depression were recruited from the Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS),<sup>8</sup> a randomized clinical trial that enrolled patients with unipolar depression. The control group was composed of age-matched ( $\pm 5$  years) and gender-matched subjects recruited from among the students and staff of the University of São Paulo and through word-of-mouth.

The local and national ethics committees approved the study protocol and the participants provided informed written consent.

### Subjects

Patients aged between 18 and 75 years presenting unipolar depression were recruited. They presented a depressive episode of at least moderate severity (corresponding to a Hamilton 17-item depression rating scale (HDRS17) score  $\geq 17$ ), low suicidal ideation, ability to read and understand Portuguese and at least eight years of schooling. The exclusion criteria were other axis I disorders (except anxiety disorders as a comorbidity) such as bipolar disorder ( $n = 9$ ), schizophrenia

( $n = 6$ ), alcohol and substance use disorders ( $n = 2$ ); and any axis II (personality and developmental) disorders ( $n = 15$ ). Patients who presented severe, life-threatening medical conditions and concomitant neuropsychiatric disorders such as dementia, epilepsy and stroke were also excluded ( $n = 14$ ). In addition, participants needed to have been antidepressant-free for at least three weeks (five weeks for fluoxetine) at the start of the trial. Therefore, for patients using antidepressant drugs, a drug washout was performed. Benzodiazepine drugs were allowed if their use remained constant throughout the entire study and at a maximum dose of 20 mg/day (diazepam equivalent).

Controls answered a short questionnaire informing about possible psychiatric and neurological disorders and any psychotropic medication use. They were excluded if they presented important depressive symptoms.

### Assessments

The diagnoses of psychiatric disorders were confirmed by certified psychologists/psychiatrists using the Portuguese-validated version of the Mini-International Neuropsychiatric Interview (MINI).<sup>9</sup> The BDI (range: 0-63; sign: positive; minimum significant score: 0-9, normal) was used to evaluate depressive symptoms.

To evaluate anxiety and affect in our sample, the Portuguese-validated versions of the State-Trait anxiety inventory (STAI; range: 0-80; sign: positive; minimum significant score: not available, N/A) and the positive and negative affective scale (PANAS; range: 10-50; sign: positive; minimum significant score: N/A)<sup>10</sup> were applied. STAI evaluates state anxiety (A-state) and trait anxiety (A-trait), i.e. the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious, respectively. PANAS consists of two 10-item mood scales that provide independent measurements of positive affect and negative affect (PA and NA, respectively). The Portuguese-validated, self-assessment scale of the Beck Depression Inventory (BDI)<sup>10</sup> was used to evaluate depression severity. Volunteers who scored 13 or more in the BDI were not included in the control group.

Personality traits were assessed using the self-administrated Brazilian version of TCI<sup>11</sup> consisting of 240 self-descriptive true/false items, assessing four temperament dimensions: NS (range 0-40; sign: positive; minimum significant score: N/A); HA (range: 0-35; sign: positive; minimum significant score: N/A); RD (range: 0-24; sign: positive; minimum significant score: N/A); P (range: 0-8; sign: positive; minimum significant score: N/A); SD (range: 0-44; sign: positive; minimum significant score: N/A); and three character dimensions: C (range: 0-42; sign: positive; minimum significant score: N/A); and ST (range: 0-33; sign: positive; minimum significant score: N/A).

## Statistical analysis

Analyses were performed in Stata 14 for Mac (Statacorp, College Station, TX, USA). A two-tailed P of 0.05 was adopted as the threshold for statistical significance. The t test (which was used for our continuous variables because they were normally distributed) and the  $\chi^2$  test (for categorical variables) were used for descriptive analysis.

Initially, we conducted multivariate analysis of variance (MANOVA) which compared all temperament and character traits (seven dependent variables) between the controls and depressed subjects. Because the MANOVA model was significant, analyses of variance (ANOVAs) were performed to assess whether each dependent variable was statistically different between the groups. Additional ANOVAs were conducted to investigate the influence of anxiety and affect on each variable.

Finally, mediation analyses were performed to further investigate the influence of anxiety and affect on mood. There were four mediation analyses, each with a different moderator variable (A-state, A-trait, PA and NA). For all analyses, group (depressed versus control subjects) was the independent variable and HA score was the dependent variable. In accordance with previous definitions,<sup>12</sup> a mediator was identified when: 1) both the independent and dependent variables correlated with the mediator; and 2) no direct effect from the independent variable on the dependent variable was any longer observed when the mediation variable was included. Sobel-Goodman mediation tests were conducted (*sgmediation* package) to test whether a mediator carried the influence of an independent variable to a dependent variable.

## RESULTS

The groups were generally similar in clinical and demographic characteristics, except for a higher proportion of married people in the control group. Although the patients were not using antidepressant drugs, 19.5% of them were on low-dose benzodiazepines. The controls presented higher scores for PA and lower scores for NA, A-trait, A-scale and BDI than the depressed patients. In contrast, the patients with depression had higher scores for HA and lower scores for NS, P, SD, and C (Table 1).

The MANOVA revealed that the scores for personality traits were significantly different between the groups, with a large effect size (Pillai's trace  $V = 0.498$ ;  $F_{7,198} = 28$ ;  $P < 0.001$ ;  $\eta_p^2 = 0.498$ ). Separate univariate ANOVAs on the dependent variables showed that all of them, except for RD and ST, were different between the groups. However, HA and NS were no longer different between the groups when A-trait was introduced as a covariate and P was not significantly different between the groups when A-state and PA were introduced as covariates (Table 2).

Mediation analyses revealed that anxiety-trait fully mediated the relationship between the group and HA, since introduction of this variable changed the direct effect of the group on HA from significant to non-significant, and the Sobel-Goodman test revealed that the influence of the group on HA was carried, through the mediating effect of anxiety-trait (Figure 1). Moreover, anxiety-state, positive affect and negative affect were partial mediators of the influence of the group on HA, since both the direct and indirect effects in the Sobel-Goodman tests were significant (Table 3).

## DISCUSSION

In this case-control study comparing 103 antidepressant-free depressed subjects with 103 age and gender-matched controls, the combined scores for TCI were significantly different between the groups, with a large effect size. Depressed patients

**Table 1.** Clinical and demographic characteristics of the sample.

	Major depressive disorder (n = 103)	Control subjects (n = 103)
<b>Gender, n (%)</b>		
Female	69 (67)	69 (67)
Male	34 (33)	34 (33)
<b>Age, years, mean (SD)</b>	45 (13)	44 (14)
<b>Marital status, n (%)</b>		
Single	45 (43.7)	37 (36)
Married	37 (36)	61 (60)*
Divorced	18 (17.5)	5 (5)
Widowed	2 (2)	0
<b>Years of schooling, mean (SD)</b>	15 (4)	17 (4)*
<b>Beck Depression Inventory, mean (SD)</b>	31 (10)	4.3 (3.3)*
<b>Anxiety-trait, mean (SD)</b>	63 (10)	35 (7)*
<b>Anxiety-state, mean (SD)</b>	55 (11)	34 (8)*
<b>Positive affect, mean (SD)</b>	16 (6)	34 (6)*
<b>Negative affect, mean (SD)</b>	29 (10)	15 (5)*
<b>Benzodiazepine use, n (%)</b>	20 (19.5)	--
<b>Temperament and character inventory scores, mean (SD)</b>		
Novelty seeking	16.5 (5.5)	18.5 (5.6)*
Harm avoidance	25.6 (7.2)	15.4 (6.1)*
Reward dependence	14.1 (4.1)	15.1 (4.1)
Persistence	4.6 (1.9)	5.3 (1.7)*
Self-directedness	21.7 (8)	33.4 (5.9)*
Cooperativeness	29.4 (6.9)	34.1 (4.9)*
Self-transcendence	16.1 (6.8)	17.9 (6.4)

SD = standard deviation; n = number of subjects. \*Represents variables that are significantly different between groups at  $P < 0.05$ .

presented higher HA and lower SD scores, as previously observed.<sup>3</sup> This is in accordance with clinical observations showing excessive worrying, avoidant behaviors, poor goal-oriented behaviors, low confidence, and low self-esteem in cases of depression. Our patients also presented lower scores for C and P. This characteristic, along with higher scores for HA, are found in cluster C personality disorders,<sup>13</sup> which are the most common personality disorders observed among depressed patients.<sup>14</sup> Finally, we observed that the patients presented lower NS; however, this characteristic has not been found previously.<sup>3</sup>

The difference in TCI between the depressed and control participants persisted after adjustment for trait-state anxiety (STAI) and for positive or negative affect (PANAS). Nonetheless, separate analysis of each dimension revealed some distinct findings. Remarkably, the participants did not present any difference in HA scores when the comparison was adjusted for trait anxiety, which fully mediated the influence of the group on HA. Previous studies found that polymorphisms of the serotonin transporter gene were associated both with anxiety<sup>15</sup> and

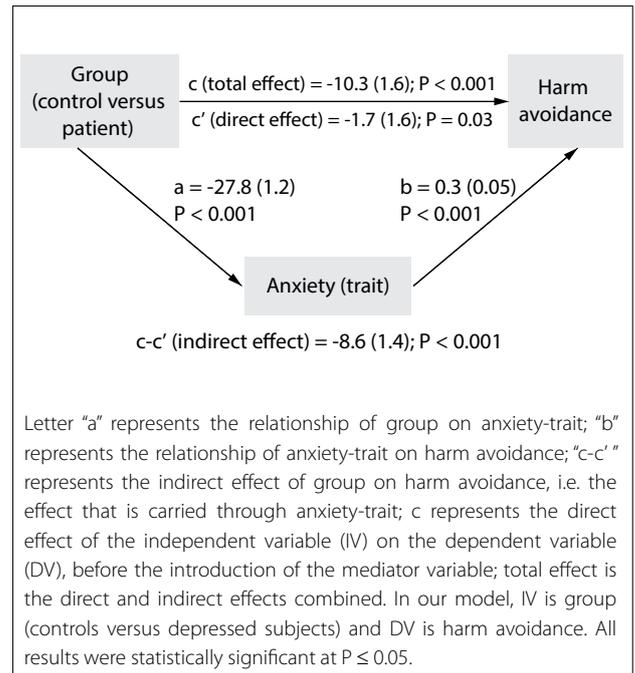


Figure 1. Mediating effect of anxiety-trait on harm avoidance.

Table 2. Univariate analyses on variances (ANOVAs) for personality traits.

Dependent variable	Unadjusted		Anxiety (trait)		Anxiety (state)		Positive affect		Negative affect	
	F	P	F	P	F	P	F	P	F	P
Novelty seeking	6.93	< 0.01	2.5	0.115	6.67	0.01	0.38	0.54	8.271	< 0.01
Harm avoidance	120.7	< 0.001	1.06	0.3	21.8	< 0.001	10.97	< 0.001	34.15	< 0.001
Reward dependence	2.89	0.091	8.07	< 0.01	3.54	0.06	3.96	0.048	2.8	0.09
Persistence	7.06	< 0.01	6.56	0.01	3.811	0.052	0.43	0.83	6.5	0.01
Self-directedness	144.04	< 0.001	5.57	0.02	42.8	< 0.001	14.2	< 0.001	45.67	< 0.001
Cooperativeness	31.72	< 0.001	11.48	0.001	20.2	< 0.001	7.3	< 0.01	14.6	< 0.001
Self-transcendence	3.52	0.062	1.05	0.3	8.5	< 0.01	0.75	0.78	5.69	0.02

Values in bold represent significant results at  $P < 0.05$ .

Table 3. Results of the Sobel-Goodman tests evaluating the influence of group on harm avoidance according to different mediators.

	Mediator variable					
	Anxiety (state)		Positive affect		Negative affect	
	Coef (SE)	P	Coef (SE)	P	Coef (SE)	P
a (IV --> MV)	-21.2 (1.4)	< 0.001	17.9 (0.8)	< 0.001	-13.3 (1.1)	< 0.001
b (MV --> DV)	0.19 (0.04)	< 0.001	-0.25 (0.08)	< 0.001	0.2 (0.6)	< 0.001
c-c' (indirect effect)	-4.1 (1)	< 0.001	-4.5 (1.4)	< 0.001	-3.1 (0.8)	< 0.001
c (direct effect)	-6.1 (1.3)	< 0.001	-5.6 (1.7)	< 0.001	-7 (1.2)	< 0.001
Total effect	-10.3 (0.9)	< 0.001	-10.15 (0.9)	< 0.001	-10.1 (0.9)	< 0.001

a = relationship of the independent variable (IV) on the mediator variable (MV); b = relationship of the mediator variable (MV) on the dependent variable, c-c' = represents the indirect effect of the IV on the DV, i.e., the effect that is carried through the mediator variable; c = represents the direct effect of the IV on the DV, before the introduction of the mediator variable; total effect is the direct and indirect effects combined. In our model, IV is group (controls versus depressed subjects) and DV is harm avoidance. All results were statistically significant at  $P \leq 0.05$ .

with harm avoidance behavior.<sup>16</sup> Thus, it is possible that the mediating effect observed reflected dysfunction in serotonin metabolism among participants with high HA and trait-anxiety scores. Alterations to amygdala response might also explain this finding, since chronic stress and anxiety changed amygdala responsiveness,<sup>17</sup> which is involved in regulation of harm avoidance behavior.<sup>18</sup>

Conversely, the between-group differences in SD and C persisted even after adjustment for anxiety and mood scores. This might reflect the more stable and meta-cognitive nature of character traits, which are theoretically less correlated with anxiety and affect than temperament traits.

There were more married people in the control group. This might be explained by the greater incapacity of depressed patients in establishing or maintaining long-term relationships. Nonetheless, this issue could have partly influenced the results, since being married is associated with greater subjective wellbeing.<sup>19</sup>

Although the patients were antidepressant-free, 19.5% of them were on low-dose benzodiazepines. A recent study enrolling a large sample of 8,646 individuals showed that benzodiazepine use is associated with higher HA and lower SD. However, this association is larger in individuals who present benzodiazepine abuse or dependence.<sup>20</sup> Nonetheless, it is possible that our results were partly driven by the small proportion of patients on benzodiazepine use.

The limitations of our study include the several comparisons performed that might have had inflated type I errors. Therefore, our findings should be interpreted as exploratory and validated in further studies. Also, due to our study design, we cannot disentangle whether the lower scores for trait variables reflected exacerbation of symptoms during depressive episodes and whether they would persist after remission from the episode. Moreover, the controls presented longer schooling than the patients, an issue that limits the strength of evidence of our findings. Finally, another important limitation is that the control group was not evaluated by psychologists or psychiatrists through a clinical interview and/or structured questionnaire.

Our findings highlight the importance of assessment of personality traits among patients with depression, which is a matter that might be overlooked by physicians and psychiatrists. Recognition that patients with depression usually present high HA and low SD is important when making clinical diagnoses and starting treatments. Moreover, we found that anxiety trait fully moderated the association between HA and avoidance. Considering that HA carries significant burden, given that it is associated with excessive worry, pessimism and avoidance behavior, clinical approaches targeted towards anxiety trait treatment might be particularly advantageous.

## CONCLUSION

Patients with depression presented a significantly different pattern of temperament and character traits, compared with control subjects, although not all dimensions differed between the groups, particularly after considering anxiety and affect. This reflects the complex and variable association of personality and depression, which involves adaptive and dynamic mental and biological systems that are interrelated at different levels. Particularly, the fully mediation effects of anxiety trait on the association between depression and harm avoidance should be further explored in longitudinal studies.

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# Non-invasive brain stimulation and computational models in post-stroke aphasic patients: single session of transcranial magnetic stimulation and transcranial direct current stimulation. A randomized clinical trial

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## KEY WORDS:

Aphasia.

Stroke.

Speech disorders.

Transcranial direct current stimulation.

Transcranial magnetic stimulation.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Patients undergoing the same neuromodulation protocol may present different responses. Computational models may help in understanding such differences. The aims of this study were, firstly, to compare the performance of aphasic patients in naming tasks before and after one session of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) and sham, and analyze the results between these neuromodulation techniques; and secondly, through computational model on the cortex and surrounding tissues, to assess current flow distribution and responses among patients who received tDCS and presented different levels of results from naming tasks.

**DESIGN AND SETTING:** Prospective, descriptive, qualitative and quantitative, double blind, randomized and placebo-controlled study conducted at Faculdade de Ciências Médicas da Santa Casa de São Paulo.

**METHODS:** Patients with aphasia received one session of tDCS, TMS or sham stimulation. The time taken to name pictures and the response time were evaluated before and after neuromodulation. Selected patients from the first intervention underwent a computational model stimulation procedure that simulated tDCS.

**RESULTS:** The results did not indicate any statistically significant differences from before to after the stimulation. The computational models showed different current flow distributions.

**CONCLUSIONS:** The present study did not show any statistically significant difference between tDCS, TMS and sham stimulation regarding naming tasks. The patients' responses to the computational model showed different patterns of current distribution.

## INTRODUCTION

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are safe non-invasive techniques that present different characteristics. TMS equipment is more expensive, its stimulation is more focal, it has better temporal resolution and its accuracy is of the order of milliseconds while that of tDCS is of the order of minutes. TMS generates muscle contraction and provides a sound stimulus during its application, while TDCS is more easily applicable, does not generate muscle contraction and does not provide back-sound stimulus. In applications of TMS, rare cases of convulsion have been reported although mild adverse effects (such as transient headache) may occur. The literature on tDCS does not report any correlation with seizure but it describes mild adverse effects such as transient headache. Both techniques can influence distant cortical and subcortical areas beyond the stimulation area, due to trans-synaptic effects. The current direction may differ in subjects with or without brain injury.<sup>1,2</sup>

The concept of inter-hemispheric competition for language and motor deficits after stroke lies behind the principle of neuromodulation. The aim is to facilitate increased brain activity in the injured hemisphere, while favoring inhibition of cortical activity in the healthy hemisphere.<sup>3-5</sup>

Investigations using one session of TMS or tDCS have suggested that use of these techniques among aphasic patients after stroke has a relationship with language improvement. Thus, these techniques may be promising for speech rehabilitation in cases of aphasic syndromes.<sup>6,7</sup> Recent evidence from noninvasive brain stimulation (NIBS) has indicated that neuromodulation in consecutive sessions might be a beneficial tool for improving language skills among aphasic patients.<sup>8,9</sup>

Inter-individual differences in response to NIBS remain an important area of investigation and a hurdle to be surmounted for achieving clinically efficacious treatment. The reasons for different responses shown in studies are not well-defined, but may relate to the distribution of electric current through the brain and surrounding tissues. Thus, development of computational models simulating the current distribution of tDCS in patients with different clinical responses makes it possible to accurately review current patterns in tDCS applications and to understand clinical outcomes better.<sup>10</sup>

## OBJECTIVES

The aim of this study was firstly to describe the responses of significantly aphasic post-stroke patients to naming tasks, before and after one application of tDCS, TMS or sham, and to compare these neuromodulation techniques; secondly, the intention was to describe current distribution in the cortex and surrounding tissues through computational model stimulation, among patients who showed different results in naming tasks after tDCS.

## METHODS

This was a prospective, qualitative and quantitative, double blind, randomized and placebo-controlled study. It was approved by the research ethics committee of Santa Casa de São Paulo under registration number 169/10. Patients were randomized to receive the three forms of stimulation: tDCS, TMS and sham. The randomization was made by statistic orientation in three weeks (**Table 1**).

The sample included post-stroke patients of both sexes who had suffered a left hemisphere ischemic stroke at least six months earlier. These patients were recruited in the Neurology Department and the sample size was calculated statistically. The diagnosis of aphasia was made by a speech pathologist before neuromodulation, and a medical neuroimaging evaluation was also performed. The lesions were located not only in the frontal lobe but also in the parietal lobe, temporal lobe and subcortical areas.

For the purposes of the present study, clinical and diagnostic findings of aphasia were given preference, rather than topographic data. The inclusion criteria were that the subjects needed to present Broca or anomic aphasia without comorbidities such as dysarthria or apraxia of speech and without previous speech and language therapy. Patients with any clinically significant or unstable medical or psychiatric disorder, any history of substance abuse or any neuropsychiatric comorbidity were excluded. The aphasia classification was based on speech and language pathology standards.<sup>11-13</sup>

Direct current stimulation was transferred through a saline-soaked pair of surface sponge electrodes (10 cm x 10 cm and 5 cm x 7 cm) and was delivered by means of a specially developed direct current stimulator. The electrode placement was as follows: the anode (10 cm x 10 cm) was over the Broca area and

the cathode (5 x 7 cm) was centered horizontally over the F8 of the 10-20 system.<sup>14</sup> tDCS was applied for 20 minutes at a current intensity of 2 mA. TMS was carried out in the right hemisphere, in the area homologous to Broca's area, located by means of the 10-20 system (F8), with a frequency of 1 Hz, using 90% of the motor threshold for 20 minutes. The threshold corresponded to a lower-intensity stimulus applied to the right hemisphere motor area, which causes contraction of the left-side first interosseous muscle, observed through electromyography (EMG), using surface electrodes. The motor threshold was recalculated after test assessments. Motor cortex excitability was measured by means of the motor evoked potential (MEP) and silent period (SP) before starting and immediately at the end of stimulation.<sup>15</sup>

The tDCS placebo consisted of the same stimulator apparatus as described above, with the stimulator turned on for 20 seconds to mimic the effect of stimulation. The TMS placebo comprised a specific coil, with a screen that did not allow passage of the magnetic field but produced a sound stimulus of similar characteristics.

The subjects did the Boston Naming Test<sup>16</sup> before and after each neuromodulation procedure. The patients received tDCS, TMS or placebo in a silent and well-lit room. Their responses were recorded with a head microphone in the CronoFonos software.

An exploratory analysis verified the scores before and after each picture-naming stimulation, considering not only the picture naming but also the picture-naming strategy (i.e. the number of words correctly named plus the linguistic strategies used by the subject to achieve this) and the response time (including the response time for naming strategy and total response time). In the event of absence of responses, the time interval was replaced by 20 seconds for each item unanswered.

The Kruskal-Wallis and Wilcoxon tests were used to compare responses and variables. The data were reported as means and standard deviations. Statistical significance was taken to be a two-tailed P-value of < 0.05.

Three subjects from the first intervention were selected to receive computational models that simulated the tDCS brain current flow. The criterion for selecting them was that they should be one of the best responders, the worst responder and a control, after one session of tDCS. The response classification considered the qualitative descriptive improvement/worsening of all parameters evaluated before and after the stimulation.

To calculate the tDCS-induced electric fields, a 3D model for the volume conductor (resolution of 1 mm<sup>3</sup>) was chosen. The entire process followed a previous study.<sup>17</sup> The electrical properties of the tissues were representative of isotropic average values (in S/m): brain: 0.2; cerebrospinal fluid (CSF): 1.65; skull: 0.01; and scalp: 0.465. The muscle, fatty tissue, eye and blood vessel compartments paralleled the same scalp tissue. The anode (10 cm x 10 cm) was placed over the Broca area and the cathode (5 cm x 7 cm) was

centered horizontally over the F8 of the 10-20 system. To implement the model, the commercially available Comsol Multiphysics 3.5 finite element (FE) package (Comsol Inc., MA, USA) was used, following a method that had already been described<sup>18</sup>. The results were compared on the same scale after the simulation and the current density ranged from 0 V/m to 0.522 V/m.

## RESULTS

Thirteen patients were included in this study (53.8% men), with a mean age of 56 years and with elementary and high school educational levels. All the patients received active transcranial direct current stimulation, transcranial magnetic stimulation or sham, with no adverse effects reported. **Table 2** describes the subject data and **Table 1** shows the randomization results.

**Table 3** details the statistical results from the Wilcoxon test on mean performance in the naming test before and after stimulation. These assessments indicated that there was a statistically significant difference in the picture-naming task after a single application of

tDCS, and this was also seen from the sham. Comparison of the three techniques using the Kruskal-Wallis test did not demonstrate which one was more effective, because no statistical difference was observed between them (**Table 3**).

Descriptive analysis was conducted on the patients' overall performance, from before to after stimulation. Four subjects demonstrated improvement in all tDCS parameters (patients 1, 9, 10 and 13) and subject #10 was randomly selected as the best responder. Since subject #12 did not show any improvement, this patient was considered to be the worst responder. The subject randomly selected as the control revealed intermediate results, with improvement in two parameters (**Table 4**).

There were differences in the peak intensities and distributions of the cortical electric field (current density) between the subjects, as demonstrated in **Figure 1**.

The results shown in **Figure 1** indicate that the subject with the best result (ranked first) showed less diffuse distribution in the right frontal lobe, with peaks in the area homologous to Broca's area and in the orbital gyri. The subject with the worst result (ranked third) showed diffuse distribution over the right temporal and frontal lobes, with peaks in the right temporal lobe. The control subject (ranked second) had an intermediate result, showing diffuse

**Table 1.** Description of the randomization

Subject	First week	Second week	Third week
1	Sham	TMS	tDCS
2	Sham	tDCS	TMS
3	TMS	Sham	tDCS
4	TMS	tDCS	Sham
5	tDCS	TMS	Sham
6	tDCS	Sham	TMS
7	Sham	TMS	tDCS
8	Sham	tDCS	TMS
9	TMS	Sham	tDCS
10	TMS	tDCS	Sham
11	tDCS	TMS	Sham
12	tDCS	Sham	TMS
13	tDCS	TMS	Sham

TMS = transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.

**Table 2.** Description of the patients

Subject	Sex	Age	Education	Aphasia
1	Female	26	High school	Anomic
2	Male	68	Elementary school	Anomic
3	Female	20	High school	Broca
4	Female	50	Elementary school	Broca
5	Female	75	Elementary school	Anomic
6	Male	77	Elementary school	Anomic
7	Male	48	Elementary school	Anomic
8	Male	58	Elementary school	Anomic
9	Male	65	Elementary school	Broca
10	Male	67	Elementary school	Broca
11	Female	42	Elementary school	Anomic
12	Male	77	Elementary school	Broca
13	Female	60	Elementary school	Broca

**Table 3.** Mean performance in naming tasks from before to after stimulation (Wilcoxon test) and comparison of the techniques

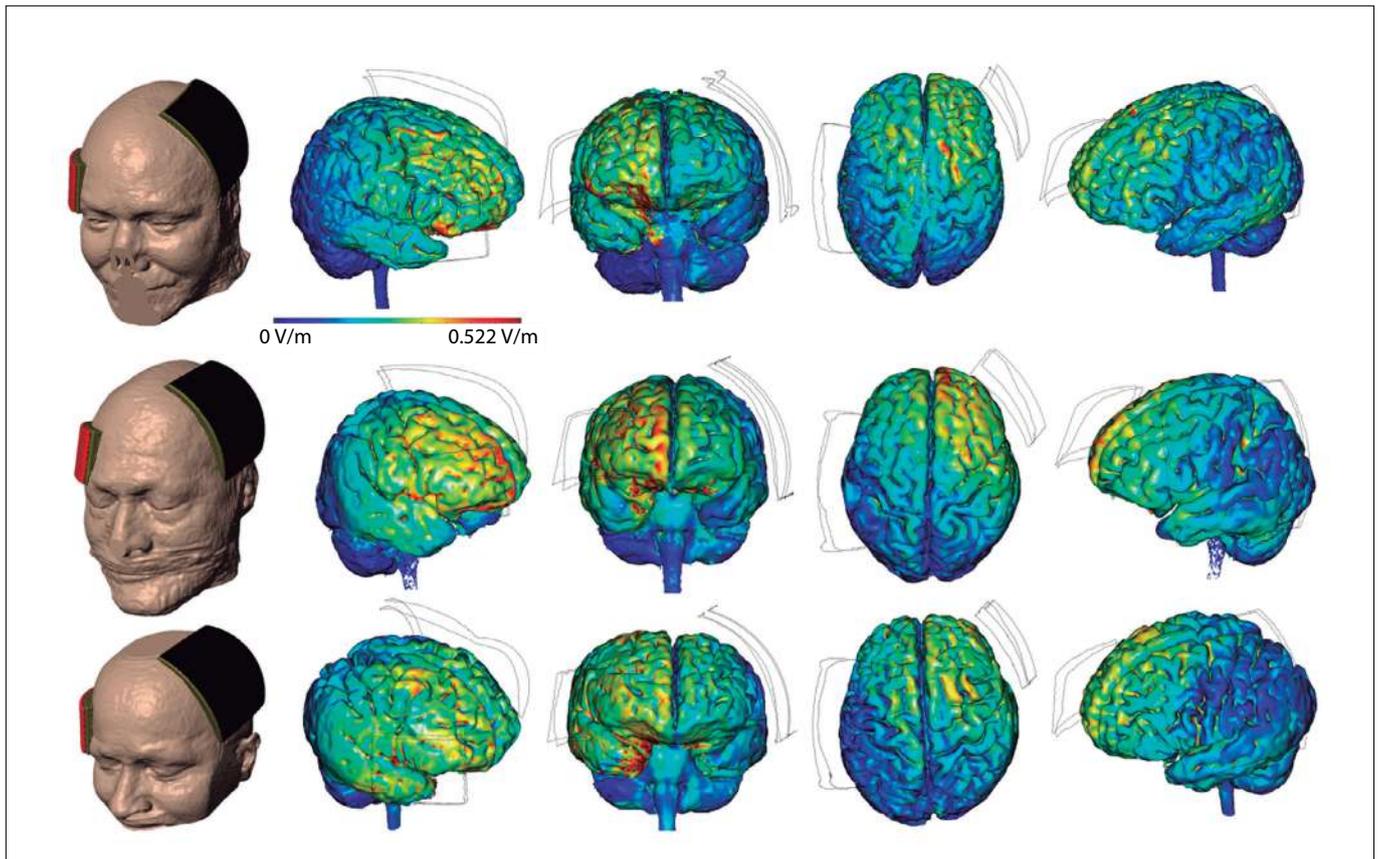
Parameters	Comparison of Sham, TMS and tDCS	Performance in naming tasks		
	P-value	Sham P-value	TMS P-value	tDCS P-value
Picture naming	0.889	0.011	0.496	0.039
Response time	0.936	0.861	0.65	0.6
Picture naming strategy	0.232	0.336	0.145	0.366
Response time strategy	0.589	0.133	0.116	0.382
Total response time	0.493	0.382	0.064	0.311

TMS = transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.

**Table 4.** Improvement in parameters evaluated

Subject	Sham	tDCS	TMS
1	4	5	2
2	1	2	2
3	1	1	0
4	1	2	0
5	4	4	3
6	3	2	4
7	3	3	3
8	4	3	2
9	4	5	5
10	3	5	4
11	3	3	3
12	4	0	3
13	0	5	4

tDCS = transcranial direct current stimulation; TMS = transcranial magnetic stimulation.



**Figure 1.** Peak intensities and distributions of cortical electric field (current density).

distribution in the right frontal lobe, with peaks in the superior frontal gyrus.

## DISCUSSION

The number of studies using non-invasive brain stimulation in language areas is increasing and most of them have involved naming tasks for aphasic subjects in more than one session of stimulation.<sup>1,7,19,20</sup> Investigations have indicated that better results were found when neuromodulation was combined with and speech therapy for language skills (especially regarding picture-naming accuracy and latency).<sup>21-26</sup>

The present study showed that there were statistically significant differences in picture-naming tasks after a single application of tDCS and after sham stimulation. The lack of detectable effect through TMS was possibly to be expected, given that high variability between subjects and weak effects regarding clinical outcomes from a single session have been shown.<sup>9,27-29</sup> Moreover, in TMS, it is difficult to precisely locate the right place to apply the stimulus and small variations in coil positioning may generate stimulation in different regions.<sup>30</sup> Hence, neuronavigation may help to determine the best location for the stimulus and improve the outcomes from TMS.

In neurorehabilitation, the challenge is magnified by inter-individual differences in injuries, along with slow and variable recovery rates even with effective treatment. Hamilton et al.<sup>31</sup> suggested that the difficulty in knowing precisely which brain regions are affected by tDCS was one of the factors that limit expansion of use of this technique. One theory that could explain tDCS results is the current flow distribution. In this regard, computational models can predict the current flow density and may be an option for understanding the results or even for elaborating electrode setups.<sup>17,18</sup> In the present study, computational models were used in post-hoc analysis and showed that the current flow distribution in the cortex differed among patients with different results. However, the number of patients in this study, which was calculated statistically, was too limited to prove this supposition.

## CONCLUSIONS

The first intervention did not show any statistically significant difference between tDCS, TMS and sham stimulation in any of the naming tasks and it was not possible to compare the techniques. Computational model procedures showed different current flow patterns among patients with different results from tDCS. This study supports the notion that the current flow

may explain the different outcomes from the first intervention. However, the number of patients in this study was too limited to prove this supposition.

The limitations resulting from use of a single session of neuromodulation and the small number of subjects enrolled in the present study need to be taken into account. It would be advisable to conduct prospective controlled clinical trials with higher numbers of patients and multiple sessions of stimulation in order to establish a more precise approach and to compare tDCS and TMS.

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# Cardiovascular emergencies in primary care: an observational retrospective study of a large-scale telecardiology service

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## KEY WORDS:

Emergencies.  
Primary health care.  
Cardiovascular diseases.  
Telemedicine.  
Electrocardiography.

## ABSTRACT

**BACKGROUND:** Electrocardiograms (ECGs) are an essential examination for identification and management of cardiovascular emergencies. The aim of this study was to report on the frequency and recognition of cardiovascular emergencies in primary care units.

**DESIGN AND SETTING:** Observational retrospective study assessing consecutive patients whose digital ECGs were sent for analysis to the team of the Telehealth Network of Minas Gerais.

**METHODS:** Data from patients diagnosed with cardiological emergencies in the primary care setting of 750 municipalities in Minas Gerais, Brazil, between March and September 2015, were collected via telephone contact with the healthcare practitioner who performed the ECG. After collection, the data were subjected to statistical analysis.

**RESULTS:** Over the study period, 304 patients with cardiovascular emergencies were diagnosed within primary care. Only 73.4% of these were recognized by the local physicians. Overall, the most frequent ECG abnormalities were acute ischemic patterns (44.7%) and the frequency of such patterns was higher among the ECGs assigned as emergency priority ( $P = 0.03$ ). It was possible to obtain complete information on 231 patients (75.9%). Among these, the mean age was  $65 \pm 14.4$  years, 57.1% were men and the most prevalent comorbidity was hypertension (68.4%). In total, 77.9% were referred to a unit caring for cases of higher complexity and 11.7% of the patients died.

**CONCLUSION:** In this study, cardiovascular emergencies were misdiagnosed in primary care settings, acute myocardial ischemia was the most frequent emergency and the mortality rate was high.

## INTRODUCTION

Cardiovascular diseases are the main cause of mortality in the world, representing 32% of deaths worldwide in 2015.<sup>1</sup> Following the global trend, cardiovascular diseases are also the leading cause of mortality in Brazil, representing 27% of all deaths in 2014.<sup>2</sup> Because of the high socioeconomic impact and high morbidity and mortality of chronic conditions, diagnosis, management and follow-up of these patients is a priority for the Brazilian national healthcare system (Sistema Único de Saúde, SUS).<sup>3,4</sup>

The Brazilian public healthcare system is composed of a hierarchical structure made up of three levels dealing with cases of increasing complexity: primary, secondary and tertiary care. The aim of the system is to provide integrated universal (free access) care to meet the healthcare needs of the Brazilian population.<sup>5</sup> Thus, primary care is the basis of the healthcare system and acts as a gatekeeper.<sup>6</sup> This setting is responsible for assessment of diseases and risks in a specific region and for developing long-term action plans.<sup>7</sup> In emergency cases, two types of facility have been set up to receive patients: emergency care units, which deal with cases of intermediate complexity and are usually available in medium-size cities; and local hospitals, which are settings for dealing with cases of high complexity and are usually available in larger cities.<sup>8</sup>

Regarding transportation of patients to proper facilities, Brazil used the French mobile emergency medical service as a template for developing its own mobile emergency medical service (Serviço de Atendimento Móvel de Urgência, SAMU). Currently, this model comprises a nationally standardized medical service that provides transportation and pre-hospital care for emergencies at any time on any given day.<sup>8</sup>

However, patients with emergencies sometimes seek assistance within the primary care setting for a variety of reasons. Firstly, the emergency services still suffer from highly restricted capacity.

There is a lack of ambulances and healthcare professionals, especially in small and remote municipalities. Secondly, availability and accessibility at the community level make primary care the first contact point, sometimes even for emergency care. Lastly, some patients purposefully avoid emergency departments.

There is a lack of studies on emergencies within the primary care setting in developing countries.

## OBJECTIVE

The objective of this study was to report on the frequency and recognition of cardiovascular emergencies in primary care units, using the database of a public telehealth service.

## METHODS

### Study design and subjects

This was an observational retrospective study in which consecutive patients whose digital electrocardiograms (ECGs) were sent for analysis to the team of the Telehealth Network of Minas Gerais (TNMG) were assessed. This study used data from patients diagnosed with cardiological emergencies between March 2015 and September 2015.

The TNMG is a Brazilian public telehealth service that was formed through a partnership among seven public universities in 2005.<sup>9</sup> Given the impact of cardiovascular diseases, the unequal concentration of medical specialists that prevails in large urban centers and the lack of electrocardiogram machines in remote municipalities, the service initially focused on tele-electrocardiography.<sup>10,11</sup> For patients assisted at primary care units in small and remote municipalities, their digital ECGs are recorded and transmitted through the internet to the TNMG center for remote analysis by a specialized team. This service currently provides support for primary healthcare settings in 780 out of the 853 municipalities in the state of Minas Gerais, Brazil. This project has proved to be cost-effective and has prevented unnecessary referral to services in other municipalities.<sup>12</sup>

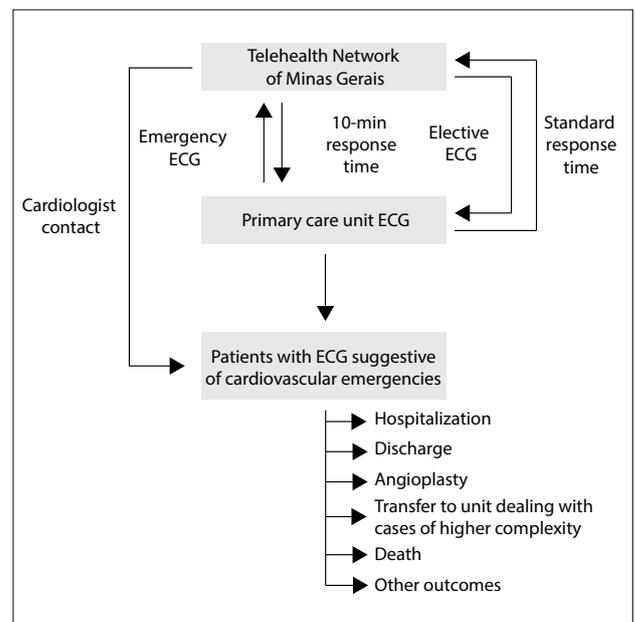
To record ECGs, the local healthcare practitioner uses special software that allows the examination to be linked to the patient's clinical data (height, weight, risk factors, medications in use, signs and symptoms) in order to increase the accuracy of the interpretation. After the digital ECG has been recorded, it is uploaded in the TNMG website (<http://www.telessaude.hc.ufmg.br>). Subsequently, the examination is received by the TNMG analysis center, where it is distributed to on-duty cardiologists who are responsible for analyzing the ECGs in accordance with standardized criteria. All examinations sent for analysis to TNMG on weekdays before 8:00 pm are evaluated on the same day, while others are dealt with on the next business day.

The primary care practitioner who records the ECG can select the priority level: emergency or elective. Emergency examinations are analyzed within 10 minutes, while elective ones are assessed

within 4 hours. An on-duty nursing technician is responsible for the operational management of clinical services. After a TNMG cardiologist has diagnosed a cardiological emergency situation based on the clinical data and the ECG, the nursing technician contacts the primary care unit to make a teleconsultation via internet or telephone call to guide the immediate management of the case (Figure 1). If needed, the cardiologist can request additional traces to analyze dynamic electrocardiographic changes, from the attending primary care physician.

For the purposes of this study, ECG abnormalities suggestive of acute myocardial ischemia, Mobitz II atrioventricular block, complete heart block, ventricular tachycardia, atrial fibrillation, atrial flutter with fast ventricular response, supraventricular tachycardia (atrioventricular nodal reentrant tachycardia or atrioventricular reciprocating tachycardia) and other electrocardiographic signs consistent with the clinical information were considered to be cardiological emergencies. The acute ischemic patterns included:

1. Symmetrical T-waves with increased amplitude, or symmetrical and pointed T-wave inversion;
2. ST segment elevation of at least 1 mm at the J-point, with superior convexity in this segment, in two contiguous leads that explored the region involved, for all leads other than leads V1-V3; and for leads V1-V3, ST-segment elevation in females  $\geq 1.5$  mm, in men over 40 years  $\geq 2.0$  mm and in men younger than 40 years  $\geq 2.5$  mm; and
3. Depression of the J-point and ST segment, such that it is horizontal or descending  $\geq 0.5$  mm in two contiguous leads, measured 60 ms after the J-point.<sup>13</sup>



**Figure 1.** Flowchart of patient and electrocardiogram (ECG) management and outcomes.

## Data collection

Five trained researchers used a standardized questionnaire to collect patient data through telephone contact with the healthcare professional who performed the ECG in the primary care unit. The survey covered the following topics:

- Medications and comorbidities, when this information had not been supplied;
- Management after diagnosis (pharmacotherapy used in the primary care unit, referral to a unit dealing with cases of higher complexity, hospitalization, pacemaker implantation, thrombolysis and/or angioplasty);
- Outcome (or death).

In some of the cases, it was possible to contact the patient directly, and the same questionnaire was applied to them. Additionally, demographic and socioeconomic aspects of the patients' municipality of origin were also assessed.<sup>14</sup> The human development index (HDI) was used to provide socioeconomic information on the municipalities. This index comprises three indicators: life expectancy at birth, years of schooling and gross national income (GNI) per capita.<sup>15</sup>

## Statistical analysis

Categorical variables were presented as absolute and relative proportions and quantitative variables as central trend measurements

and variability. The associations between variables were assessed using the chi-square test or Fisher's exact test, when indicated, for categorical variables; Student's t test for quantitative variables with normal distribution; and the Mann-Whitney test for quantitative variables without normal distribution. The normality of the quantitative variables was evaluated by means of the Kolmogorov-Smirnov test. The significance level for all tests was taken to be 0.05. Data management and statistical analyses were performed using the IBM SPSS software for Windows, version 21.0 (IBM Corp, Armonk, NY, USA). This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

## RESULTS

During the study period, ECGs on 260,879 patients were recorded and then analyzed by the cardiologists of the TNMG, and 304 of them (0.1%) were diagnosed as emergencies. Considering this sample, 71% had been classified as an emergency in the primary care setting and 29% as an elective examination (which the primary care physician had not recognized as a cardiology emergency).

The total frequency of electrocardiographic abnormalities and the frequency stratified according to priority are presented in **Table 1**. Acute ischemic patterns were the most frequent finding, comprising 44.7% of all the cases, followed by atrial fibrillation or flutter with high ventricular response (20.6%). The frequency of acute

**Table 1.** Frequency of electrocardiographic abnormalities and their stratification according to whether these were recognized as emergencies by the primary care practitioner

Electrocardiographic abnormalities	Total (n = 304)	Emergency (n = 223)	Elective (n = 81)	P-value
<b>Cardiological emergencies</b>				
Acute ischemic patterns	136 (44.7)	108 (48.4)	28 (34.5)	0.03
Atrial fibrillation and flutter with high ventricular response	61 (20.6)	42 (18.8)	19 (23.4)	0.41
Complete atrioventricular block	41 (13.4)	26 (11.6)	15 (18.5)	0.13
Supraventricular tachycardia*	26 (8.5)	18 (8.7)	8 (9.8)	0.64
Ventricular tachycardia	18 (5.9)	13 (5.8)	5 (6.1)	0.99
Second-degree atrioventricular block	20 (6.5)	10 (4.4)	10 (12.3)	0.03
<b>Other abnormalities in the same electrocardiogram</b>				
Left anterior superior divisional block	47 (15.4)	29 (13.4)	18 (22.2)	0.07
Right bundle branch block	47 (15.4)	28 (12.5)	19 (23.4)	0.03
Unspecific ventricular repolarization patterns	44 (14.4)	32 (14.3)	12 (14.8)	1.00
Secondary alterations in ventricular repolarization	37 (12.1)	23 (10.3)	14 (17.2)	0.11
Ventricular extrasystoles	20 (6.5)	12 (5.3)	8 (9.8)	0.19
Left bundle branch block	14 (4.6)	11 (4.9)	3 (3.7)	0.89
Supraventricular extrasystoles	12 (3.9)	8 (3.5)	4 (4.9)	0.84
Previous acute myocardial infarction	10 (3.2)	9 (4.3)	1 (1.2)	0.39
Right bundle branch conduction disturbance	11 (3.6)	10 (4.4)	1 (1.2)	0.32
Primary alterations in ventricular repolarization	7 (2.3)	5 (2.2)	2 (2.4)	0.90
Atrial fibrillation with low response	6 (1.9)	4 (1.7)	2 (2.4)	0.70
Other findings <sup>†</sup>	25 (8.2)	21 (9.4)	4 (4.9)	0.30

\*Supraventricular tachycardia: atrioventricular nodal reentrant tachycardia or atrioventricular reciprocating tachycardia.

<sup>†</sup>Other findings included sinus arrhythmia, first-degree atrioventricular block, sinus bradycardia, atrial fibrillation, defective pacemaker, left ventricular aneurysm, severe bradycardia, marked sinus bradycardia with junctional escape beat, atrioventricular conduction disturbance, left bundle branch conduction disorders, cardiac axis deviation to the right, pathological Q waves, poor progression of the R wave, and pacemaker, with prevalence < 1.0% each.

ischemic patterns was statistically higher in the ECGs for which the priority was assigned as emergency than in those assigned as elective (48.4% versus 34.5%,  $P = 0.03$ ), while the frequency of second-degree atrioventricular block was statistically higher in the ECGs with elective priority (12.3%) than in those with emergency priority (4.4%) ( $P = 0.03$ ). More than one main ECG finding was observed in 24 of these 304 patients (7.9%). A combination of acute ischemic patterns and atrial fibrillation or flutter with high ventricular response was observed in 13 patients (4.3%). Other less common combinations included: ischemic patterns plus complete atrioventricular block ( $n = 2$ ); ventricular tachycardia ( $n = 2$ ); Mobitz II atrioventricular block ( $n = 2$ ) or supraventricular tachycardia ( $n = 2$ ); and atrial fibrillation plus complete atrioventricular block ( $n = 1$ ) or supraventricular tachycardia ( $n = 2$ ). Regarding secondary abnormalities, the most common ones were left anterosuperior divisional block (15.4%) and right bundle branch block (15.4%). When ECGs with the two priorities were compared, right bundle branch block was more frequent in the ECGs with elective priority (23.4%) than in those with emergency priority (12.5%) ( $P = 0.03$ ).

It was possible to obtain complete information on 231 patients (75.9%) by telephone. Of these, 57.1% were men, and the mean age was  $64.9 \pm 14.4$  years. The most common comorbidity was hypertension (68.4%) and the most frequently used drug classes were diuretics (36.3%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (35.5%). Only 11.7% of the patients did not use any drugs until the day of the examination (Table 2).

With regard to management, the most frequent measures taken were referral to a unit dealing with cases of higher complexity (77.9%) and referral to a cardiologist (27.7%). Other measures included: hospitalization (27.3%), cardiac catheterization (13.9%) with or without percutaneous coronary intervention (PCI; in total, 8.2% underwent PCI), pacemaker implantation (11.7%), pharmacotherapy (6.5%), additional work-up (3.9%), referral to an intensive care unit (1.7%) and refusal of treatment (1.7%). This distribution was relatively similar when stratified according to the most frequent ECG diagnosis (Table 3). In total, 11.7% of the patients died: 10.4% of the patients with atrial fibrillation or flutter with accelerated ventricular response; 11.1% of patients with complete atrioventricular block; 14.5% of the patients with acute ischemia; and 13.3% of the patients with ventricular tachycardia. No patients with supraventricular tachycardia died.

Among all the ECGs that the primary care practitioners classified as having elective priority, it was possible to obtain information regarding the outcome in 60 cases (74.1%). The most common outcomes were: referral to a unit dealing with cases of higher complexity (80.0%) and referral to a cardiologist (35.0%). It should be noted that it was possible to have more than one outcome for each patient: for example, a patient could firstly be referred to a

unit dealing with cases of higher complexity and then be referred to a cardiologist at discharge.

Considering the social and economic data on the municipalities where the examinations were performed, the median human development index (HDI) was 0.667 (interquartile range 0.638-0.696), the median percentage of the population in poverty was 15.9% (interquartile range 7.9-27.5) and in extreme poverty, 3.9% (interquartile range 1.4-11.13) and the median population per municipality was 9,014 inhabitants (interquartile range 5,594-16,399).

**Table 2.** Self-declared health conditions of the patients with cardiovascular emergencies ( $n = 231$ )

Health condition characteristics	n (%)
<b>Age (years)</b>	
> 18	2 (0.9)
18-64.9	108 (46.7)
≥ 65	115 (49.8)
Not informed	6 (2.6)
<b>Male sex</b>	132 (57.1)
<b>Comorbidities</b>	
Hypertension	158 (68.4)
Diabetes mellitus	42 (18.2)
Dyslipidemia	29 (12.6)
Obesity	17 (7.4)
Chagas disease	15 (6.5)
Chronic pulmonary obstructive disease	7 (3.0)
Hypothyroidism	6 (2.6)
Coronary artery disease	4 (1.7)
Venous insufficiency	3 (1.3)
<b>Additions</b>	
Smoking	28 (12.1)
Alcohol consumption	8 (3.5)
<b>Previous events</b>	
Acute myocardial infarction	9 (3.9)
Stroke	6 (2.6)
<b>Family history of coronary heart disease</b>	19 (8.2)
<b>Medication in use</b>	
Diuretics	84 (36.3)
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	82 (35.5)
Beta blockers	53 (22.9)
Anticoagulants	41 (17.7)
Statins	35 (15.1)
Oral diabetics	23 (9.9)
Calcium channel blockers	20 (8.6)
H <sub>2</sub> blockers/proton pump inhibitors	18 (7.8)
Antiarrhythmics	17 (7.4)
Digoxin	12 (5.2)
Antiplatelets	10 (4.3)
Isosorbide	9 (3.9)
Benzodiazepines	8 (3.5)
Anticonvulsivants	8 (3.5)
Spironolactone	8 (3.5)
No medication in use	27 (11.7)

## DISCUSSION

This study demonstrated that there were patients with cardiovascular emergencies who sought assistance within primary care. In 29% of these cases, the physicians did not recognize these life-threatening conditions, i.e. these were situations of misdiagnosis. The most prevalent electrocardiographic abnormalities in cardiovascular emergencies in these Brazilian primary care centers were acute ischemic patterns, followed by atrial fibrillation and flutter with high ventricular response, complete atrioventricular block, ventricular tachycardia and second-degree branch block.

Provision of emergency care is an integral part of general practice. In a review on the management of emergencies in general practice, Ramanayake et al.<sup>16</sup> stated that “provision of timely, effective, proper and compassionate care requires knowledge, proper training, confidence, experience, trained supportive staff, equipment and medications.” Primary care physicians should be able to carry out at least initial pre-hospital management.<sup>16</sup> However, there is a lack of good evidence on the topic of emergency preparedness.

A survey showed that only 19% of family physicians had been trained in pediatric advanced life support.<sup>17</sup> To the best of our knowledge, there are no studies on training in adult advanced life support. In this light, lack of training is one of the reasons that may explain the lack of recognition of almost one third of cardiovascular emergencies. Although the patients' clinical data was generally not provided by the primary care practitioner, we hypothesized that the severity of the cases of patients with critical presentation and poorer prognosis was more easily recognized. This could explain our observation of higher mortality rates among patients whose

severe conditions were promptly recognized by the clinician (who then requested higher ECG priority).

In Brazil, periodic training in emergency care is not the reality within primary care. It is a challenge for primary care physicians to be up-to-date and competent in every emergency that they may face in the primary care setting, taking into account the wide spectrum of problems and the rarity of some of the emergencies encountered.<sup>18</sup> The whole team should be trained to manage such cases and each primary care practitioner should be familiar with his/her own role in the team.<sup>16</sup> The ERICO study highlighted the importance that primary care has in relation to receiving cardiovascular emergency cases and managing the pre-hospital care for these cases. In that study, 1,085 patients with acute coronary syndrome who were admitted to the university hospital of the University of São Paulo were assessed and it was demonstrated that patients who sought primary care assistance first were more likely to receive early aspirin treatment (within 3 hours) than were those who came directly to the hospital. On the other hand, 24.4% of the study participants did not receive aspirin until arriving at the hospital, although this medication is available within primary care.<sup>19</sup>

With regard to management of emergency conditions within primary care, some of them, such as acute asthma attacks or hypoglycemia, could be managed entirely within the primary care setting, but most of the cardiovascular emergencies needed to be transferred following initial management.<sup>16</sup> In the present study, it was expected that all patients would be transferred to a unit dealing with cases of higher complexity, but this did not happen, even in cases of suspected acute coronary syndrome and third/Mobitz II second-degree atrioventricular block. Early

**Table 3.** Frequency of management after diagnosis and outcomes stratified by the most prevalent electrocardiographic diagnoses observed

Diagnosis	AF or flutter (n = 48)	Complete AV block (n = 45)	Acute ischemia (n = 110)	Ventricular tachycardia (n = 15)	SVT* (n = 21)
Discharge <sup>†</sup>	6 (12.5)	5 (11.1)	19 (17.3)	2 (13.3)	5 (23.8)
Angioplasty	1 (2.1)	0 (0.0)	19 (17.3)	0 (0.0)	0 (0.0)
Catheterization	1 (2.1)	0 (0.0)	30 (27.3)	1 (6.7)	0 (0.0)
Referral to a cardiologist	14 (29.2)	10 (22.2)	34 (30.9)	3 (20.0)	6 (28.6)
Patient refusal	1 (2.1)	1 (2.2)	1 (0.9)	0 (0.0)	1 (4.8)
Pharmacotherapy	7 (14.6)	1 (2.2)	1 (0.9)	1 (6.7)	7 (33.3)
ICD	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Pacemaker implantation	0 (0.0)	24 (53.3)	2 (1.8)	1 (6.7)	0 (0.0)
Hospitalization	15 (31.3)	9 (20.0)	31 (28.2)	6 (40.0)	5 (23.8)
Intensive care	0 (0.0)	0 (0.0)	3 (2.7)	1 (6.7)	0 (0.0)
Improvement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
Additional work-up	2 (4.2)	3 (6.7)	2 (1.8)	2 (13.3)	2 (9.5)
Drug withdrawal	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Transfer to a unit dealing with cases of higher complexity	35 (72.9)	35 (77.8)	91 (82.7)	11 (73.3)	15 (71.4)
Valvuloplasty	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Death	5 (10.4)	5 (11.1)	16 (14.5)	2 (13.3)	0 (0.0)

Values shown are n (%). AF = atrial fibrillation; AV = atrioventricular; ICD = implantable cardiac defibrillator; SVT = supraventricular tachycardia.

\*Supraventricular tachycardia refers to atrioventricular nodal reentrant tachycardia or atrioventricular reciprocating tachycardia.

<sup>†</sup>The patient was discharged immediately after the ECG diagnosis.

diagnosis and management of these conditions are of utmost importance for patients' survival.<sup>20</sup>

Liddy et al.<sup>21</sup> reported that cardiovascular diseases were the most frequent in-office emergencies seen within primary care (32.7%). These authors suggested that it was necessary to implement guidelines regarding emergencies within primary care. In Brazil, there are national guidelines for management of emergencies within primary care, but obstacles to their implementation continue to exist.<sup>22</sup> The current guidelines are not ideal, because they do not consider the regional particularities of Brazil or the social inequalities in this country.

We believe that telehealth is a low-cost and effective strategy for supporting primary care practitioners, especially those located in remote towns.<sup>23</sup> Telehealth helps to improve the quality of care and reduce socioeconomic inequalities relating to access to specialized care,<sup>24</sup> through providing analysis on examinations and teleconsultations (second opinions). In the present study, the physicians could have contacted the telehealth service to seek assistance in management of their patients, through online teleconsultations. Additionally, telehealth may also be helpful through providing continuing distance education courses.<sup>25</sup>

The results from this study have been presented to the state's health department and have led to development of some actions by the TNMG: an e-book is being produced, to explain to primary care physicians what the meaning and management of each ECG abnormality is; an online lecture on diagnosis and management of myocardial ischemia was produced; online lectures on atrial fibrillation have also been produced and an anticoagulation management system has been developed.

This study has some limitations. It was based on the emergencies detected through electrocardiogram analyses performed by cardiologists of the TNMG. The patients were from 780 different municipalities spread out across Minas Gerais, Brazil, a state that is as large as France. Unfortunately, it was not possible to perform a before-and-after study, since the service was implemented in these municipalities some years ago and there is no unified electronic register in the Brazilian health system. All the information gathered for this study was obtained through telephone contacts with the healthcare professionals who attended these patients in the primary care setting or from the TNMG system. The system made available the patients' ECGs tracings and clinical information that had been provided through anamnesis and which was forwarded together with the ECGs. For the same reason, it was not possible to assess whether the patients classified as emergencies were truly emergencies, or the degree of severity of these patients' conditions. Additionally, the outcomes could not be fully assessed, since the management of cardiovascular emergencies in remote and small municipalities in Brazil includes referral to settings that deal with cases of higher complexity. Once these patients have been admitted to such centers, they are seen by different healthcare practitioners

and it was therefore difficult to obtain further clinical information. The primary care practitioners reported data on comorbidities and medications, and this left room for underreporting or misreporting. It was not possible to access the whole sample of patients with cardiovascular emergencies that were diagnosed at that time, due to difficulties in contacting the primary care practitioners. Hence, patient mortality may have been underestimated.

## CONCLUSION

In conclusion, cardiovascular emergencies are misdiagnosed within primary care settings in Brazil, and acute myocardial ischemia is the most frequent emergency. There was a high mortality rate, but it was even higher among patients with acute ischemia and ventricular tachycardia.

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# Sensitization to cat allergen and its association with respiratory allergies: cross-sectional study

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## KEY WORDS:

Immunization.

Fel d 1 protein, *Felis domesticus* [supplementary concept].

Skin tests.

Allergy and immunology.

## ABSTRACT

Cats are a significant source of allergens that contribute towards worsening of allergic diseases. The aim of this study was to investigate the association between sensitization to cat allergens and allergic respiratory diseases. This was an observational retrospective study based on the skin prick tests results of patients at a tertiary-level hospital in São Paulo. A total of 1,985 test results were assessed. The prevalence of sensitization to cat allergen was 20% (399 patients). Our data indicated that in this population of atopic patients, a positive skin prick test result for cat allergen was not associated significantly with a diagnosis of respiratory allergy.

## INTRODUCTION

The increasing prevalence of sensitization to household allergens like dust mites, pet dander and cockroaches is the result of changes to indoor environments induced by human action. Modern lifestyles and increased time spent in enclosed environments leads to reduction in natural ventilation and, consequently, increased concentration of and exposure to allergens.<sup>1,2</sup> There is evidence showing a relationship between allergic sensitization in skin prick tests and the severity of asthma, and also showing that sensitization to allergens may precede manifestation of allergic diseases.<sup>3</sup> According to some studies, cats are a significant source of allergens that contribute towards worsening of symptoms of allergic diseases and acute asthma attacks.<sup>3</sup> There is great concern among the families of patients with respiratory allergies about keeping pets at home, and this concern is exacerbated when the desired pet is a cat. To our knowledge, there is no study on the Brazilian population assessing the association between cat sensitization and respiratory allergies.

The aim of this study was to investigate the association between sensitization to cat allergen and allergic respiratory diseases in subjects with respiratory allergy seen at a tertiary hospital in São Paulo, Brazil.

## METHODS

This was an observational retrospective study based on a review of the medical records of patients who underwent skin tests over a 12-month period at the allergy outpatient clinic of a tertiary-level hospital in the city of São Paulo (SP), in order to investigate respiratory allergies. Clinical and demographic data were collected from the study population, and only the patients with confirmed diagnoses of respiratory allergies (asthma, rhinitis, asthma associated with rhinitis, conjunctivitis and rhinoconjunctivitis) were considered for this study.

The diagnosis was confirmed based on a compatible clinical history and sensitization to aeroallergens together with clinical manifestations. Allergy skin tests were performed by means of the prick method, using standardized *Fel d 1* extract for cat allergen (FDA Allergenic, Brazil). Histamine and glycerol were used as positive and negative controls, respectively. Test results

were considered positive (i.e. the reaction was positive) when the two largest perpendicular diameters of the wheals had an average value greater than or equal to 3 mm.

For each of the diagnoses considered, we analyzed the individuals sensitized and not sensitized to cat allergen based on the results from the prick test, in order to verify whether any of the groups analyzed had a greater proportion of patients sensitized to cats. Statistical analyses using cumulative percentages from tests for asthma, rhinitis, asthma associated with rhinitis, conjunctivitis and rhinoconjunctivitis were performed. Subsequently, we used the chi-square test to determine the P-value. Values under 0.05 were considered significant. The study protocol was approved by the local ethics committee. This study was developed as part of a larger protocol approved by our institution's ethics committee (CAPPesp) on July 13, 2011, under research protocol number 0360/11.

## RESULTS

A total of 1,985 test results were assessed, predominantly from female patients. The characteristics of the patients according to their gender and age are shown in Table 1, along with the distribution according to sensitization to cat allergen. The general prevalence of sensitization to cat allergen was 20% (399 patients), of whom 1% were only sensitized to cats. Cat sensitization was detected in 20.4% of the asthmatic individuals; 19.5% of the rhinitis patients; 22.2% of the patients with asthma and rhinitis; 25% of the patients with conjunctivitis; and 24% of those with rhinoconjunctivitis. The proportion of sensitization to cat allergen (positive skin test) was not significantly higher among subjects with distinct diagnoses of respiratory allergy, as shown in Table 2.

**Table 1.** Distribution of the study population according to age and sex, and cat sensitization rate

	Number	Age in years (mean ± SD)	Cat sensitization rate (%)
Male	775	23.9 ± 19.4	19.7
Female	1210	32.3 ± 18.3	20.3
P-value*		< 0.001	0.893

SD = standard deviation; \*Pearson's chi square test.

**Table 2.** Comparison between individuals sensitized and not sensitized to cat, according to diagnoses of allergic disease

	Asthma	Allergic rhinitis	Conjunctivitis	Asthma and rhinitis	Rhinoconjunctivitis
Cat-sensitized (%)	129 (20.4)	200 (19.5%)	4 (25%)	48 (22.2%)	6 (24%)
Not cat-sensitized (%)	502 (79.6)	849 (80.5%)	12 (75%)	168 (77.8%)	19 (76%)
<b>Total (P-value*)</b>	<b>631 (0.795)</b>	<b>1,049 (0.223)</b>	<b>16 (0.623)</b>	<b>216 (0.410)</b>	<b>25 (0.624)</b>

\*Pearson's chi square test.

## DISCUSSION

A total of 1,985 skin prick tests were assessed, of which 20% were positive to cat allergen. This finding is in agreement with results from studies conducted in other countries, where sensitization rates ranged from 15 to 60% in atopic patients.<sup>1,4</sup> After comparative analysis between individuals sensitized and not sensitized to cat allergen, there was a higher proportion of allergic respiratory diseases in the group with positive skin tests. This result is also consistent with those of other authors.<sup>4,5</sup> Gulbahar et al.<sup>4</sup> investigated the prevalence of sensitization to cat dander in atopic patients and found that 44.7% had positive allergic skin test results. As in our study, sensitized patients did not show any increased risk of developing asthma. These authors observed that the prevalences of asthma in the sensitized and non-sensitized groups were 38.7% and 33.6% respectively. In our study, we found that the prevalences of asthma were 20.5% in sensitized and 31.6% in non-sensitized individuals.

The relationship between exposure to household allergens and development of sensitization and asthma has been widely studied.<sup>2</sup> Although there is a general perception that sensitization to cat allergens is associated with higher prevalence of respiratory allergy, the data from the medical literature are contradictory, such that some authors have shown that the risk of sensitization, and also the prevalence of cat allergy could be increased or decreased according to the individuals' ages and their length and level of exposure to *Fel d 1*.<sup>5</sup> It is believed that the development of sensitization is influenced by several factors, including the length of exposure and the concentration of the allergen.<sup>3</sup> There is no consensus in the literature regarding *Fel d 1*, or whether early exposure to it is related to high<sup>3-5</sup> or low<sup>2</sup> development of sensitization.

Studies on the concentrations of allergens that have the capacity to cause sensitization also present conflicting results. While some have suggested that there is a linear dose-response relationship, others have taken the view that low levels of *Fel d 1* are capable of causing sensitization and that exposure to high levels can induce tolerance.<sup>2</sup> Moreover, individual variability of sensitization and family histories of atopy have been reported to explain the variability of sensitization to cat allergen.

## CONCLUSION

Our data indicate that in a population of atopic patients, sensitization to cat allergen, as represented by a positive result from a skin prick test with cat allergen, was not associated significantly with a diagnosis of respiratory allergy.

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# Relapse of congenital thrombotic thrombocytopenic purpura, after spontaneous remission, in a second-trimester primigravida: case report and review of the literature

Recidiva, após remissão espontânea, de púrpura trombocitopênica trombótica congênita em primigesta no segundo trimestre de gestação: relato de caso e revisão da literatura

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## KEY WORDS:

Purpura, thrombotic thrombocytopenic. Anemia, hemolytic. Pregnancy, high-risk. Stillbirth. ADAM proteins

## PALAVRAS-CHAVE:

Púrpura trombocitopênica trombótica. Anemia hemolítica. Gravidez de alto risco. Natimorto. Proteínas ADAM.

## ABSTRACT

**CONTEXT:** Thrombotic microangiopathy syndrome or thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) describes distinct diseases sharing common pathological features: microangiopathic hemolytic anemia and thrombocytopenia, without any other apparent cause.

**CASE REPORT:** An 18-year-old second-trimester primigravida presented with a history of fifteen days of intense weakness, followed by diarrhea over the past six days. She reported having had low platelets since childhood, but said that she had never had bleeding or menstrual abnormalities. Laboratory investigation showed anemia with schistocytes, thrombocytopenia and hypohaptoglobulinemia. Red blood cell concentrate and platelet transfusions were performed. The hypothesis of TTP or HUS was put forward and ADAMTS13 enzyme activity was investigated. The patient evolved with increasing platelet counts, even without specific treatment, and she was discharged. One month afterwards, she returned presenting weakness and swollen face and legs, which had developed one day earlier. The ADAMTS13 activity was less than 5%, without presence of autoantibodies. Regarding the two previous admissions (at 9 and 16 years of age), with similar clinical features, there was spontaneous remission on the first occasion and, on the second, the diagnosis of TTP was suspected and plasmapheresis was performed, but ADAMTS13 activity was not investigated.

**CONCLUSION:** To date, this is the only report of congenital TTP with two spontaneous remissions in the literature. This report reveals the importance of suspicion of this condition in the presence of microangiopathic hemolytic anemia and thrombocytopenia without any other apparent cause.

## RESUMO

**CONTEXTO:** A síndrome de microangiopatia trombótica, ou púrpura trombocitopênica trombótica-síndrome hemolítica urêmica (PTT-SHU), descreve doenças diversas com clínica e achados patológicos comuns: anemia hemolítica microangiopática e trombocitopenia, na ausência de outra causa aparente.

**RELATO DO CASO:** Primigesta de 18 anos no segundo trimestre apresenta-se com quadro de 15 dias de fraqueza intensa seguida por diarreia há seis dias. Relata ter plaquetas baixas desde a infância e nega sangramentos e anormalidades menstruais. Investigação laboratorial identificou anemia com esquizócitos, plaquetopenia e hipo-haptoglobulinemia. Foi realizada transfusão de plaquetas e concentrado de hemácias. A hipótese de PTT ou SHU foi aventada e realizou-se pesquisa da atividade da enzima ADAMTS13. A paciente evoluiu com elevação das plaquetas, mesmo sem tratamento específico, tendo alta. Retornou após um mês da alta com queixa de fraqueza há um dia e inchaço de face e pernas. A atividade da ADAMTS13 foi menor que 5%, sem autoanticorpos. Nas duas internações anteriores (aos 9 e 16 anos), com quadros similares, houve remissão espontânea na primeira internação e, na segunda, o diagnóstico de PTT foi suspeitado e foi realizada plasmáfereze, porém sem a pesquisa da atividade da ADAMTS13.

**CONCLUSÃO:** Até esta data, este é único relato de TTP congênita com duas remissões espontâneas na literatura. Este relato revela a importância da suspeição desta patologia na presença de anemia hemolítica microangiopática e trombocitopenia sem outra causa aparente.

## INTRODUCTION

Thrombotic microangiopathy syndrome (TMS) or thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) describes distinct diseases sharing common pathological features: microangiopathic hemolytic anemia (defined by the presence of schistocytes in blood smears) and thrombocytopenia (with or without neurological or renal abnormalities) without any other apparent cause.<sup>1-3</sup>

The variety of presentations and lack of specific diagnostic criteria for TTP-HUS hinder and delay its recognition and treatment by means of plasmapheresis.<sup>1</sup> Children with microangiopathic hemolytic anemia, acute renal failure and thrombocytopenia have been classified as presenting hemolytic uremic syndrome (HUS). This disease is typically preceded by diarrhea and abdominal pain, caused by Shiga toxins that are produced by bacteria such as *Escherichia coli* 0157:H7. It has low mortality, and 91% of typical HUS children survive without plasmapheresis, thus suggesting that TTP and HUS are two different syndromes.<sup>1</sup> However, their diagnostic criteria are the same, and although renal failure and neurological abnormalities are characteristic of HUS and TTP, respectively, these features may never occur.<sup>1</sup>

Several conditions, such as infections, surgery and pregnancy can precipitate TMS.<sup>3</sup> Congenital TTP is the most frequent manifestation of TMS during pregnancy.<sup>3,4</sup> This is a rare disorder with only just over 100 case descriptions worldwide.<sup>5</sup> It is caused by mutations in the ADAMTS13 enzyme (“a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13”). This is a protease that cleaves von Willebrand factor, which is a multimer synthesized by endothelium that, if degradation does not occur, accumulates and thus leads to spontaneous formation of microthrombi in the microcirculation.<sup>6,7</sup> Congenital TTP is characterized by low ADAMTS13 activity in the absence of anti-ADAMTS13 autoantibodies, which are present in acquired TTP.<sup>8</sup>

The initial evaluation should investigate possible secondary causes such as pregnancy, autoimmune disease and infection by the human immunodeficiency virus. It needs to rule out other causes of microangiopathy such as neoplasia and disseminated intravascular coagulation.<sup>5</sup> Presence of a family history may suggest congenital

cases.<sup>5</sup> Its main differential diagnoses during pregnancy include disseminated intravascular coagulation and the HELLP syndrome (hemolysis, elevated liver-enzyme levels and low platelets).<sup>9</sup>

We searched the MEDLINE (via PubMed), LILACS (via BVS) and UpToDate databases for the terms: “Congenital Thrombotic Thrombocytopenic Purpura”, “Hereditary Thrombotic Thrombocytopenic Purpura”, “Familial Thrombotic Thrombocytopenic Purpura”, “Upshaw–Schulman syndrome”, “Thrombotic Thrombocytopenic Purpura”, “Microangiopathic Hemolytic Anemia”, “Pregnancy” and “ADAMTS13” (Table 1). We found 43 cases of congenital thrombotic thrombocytopenic purpura in pregnant women reported in the literature.

## Case report

An 18-year-old primigravida, with a fetus of 16 weeks of gestational age, presented to the obstetrics emergency department with a condition of intense weakness, followed by diarrhea, that she had had for 15 days. She said that she did not have any fever, headache, bleeding, seizures, neurological abnormalities, urinary abnormalities, rash or shortness of breath, and that she was not using any medications.

She reported that she had had a condition of “low platelets” since childhood (but without any bleeding and with regular menstrual cycle and flow), and that she had been admitted to this hospital (without remembering any details), where she was followed up by the hematology and nephrology departments, with discharge from the hospital three years before the present case.

In the medical files relating to this patient, we found two previous admissions to the emergency department of this hospital. At the first admission, when she was nine years old, she presented with acute hemolysis, uremia and ascites, which progressed to urosepsis and seizures. She was then kept in hospital for treatment with steroids, antibiotic therapy and peritoneal dialysis. Subsequently, she was followed up as an outpatient by the hematology department and she evolved with spontaneous and sustained normalization of platelets and hemoglobin, upon which she was discharged with orientations.

At the second admission, she was 16 years old and presented with abdominal pain, vomiting and hematuria. In the investigation,

**Table 1.** Summary of search strategies conducted on January 15, 2017

Database	Search strategies	Results	Related results
MEDLINE (via PubMed)	("Purpura, Thrombotic Thrombocytopenic"[Mesh] OR Purpura, thrombotic thrombocytopenic) AND ("Pregnancy"[Mesh] OR Pregnancy). Filters: Case Reports	227	43
LILACS (via BVS) (this was a secondary database)	tw:(((mh:("Purpura, Thrombotic Thrombocytopenic")) OR ((tw:("púrpura trombótica trombocitopénica")) OR (tw:("púrpura trombocitopênica trombótica")))) AND ((mh:("Pregnancy")) OR (tw:("gestação")) OR (tw:("gravidez")) OR (tw:("embarazo")))) AND (instance:"regional") AND ( mh:("Pregnancy") AND db:("IBECs" OR "LILACS") AND type_of_study:("case_reports"))	4	0

Coombs-negative hemolytic anemia with thrombocytopenia and elevated blood urea nitrogen were found. An abdominal ultrasound showed mild alteration of renal texture. She was kept in hospital to receive a methylprednisolone pulse because of the suspicion of rapidly progressive glomerulonephritis. Presence of schistocytes in blood smears suggested a diagnosis of TTP or HUS. Plasmapheresis was performed and steroids were administered, without further investigations. Because her condition evolved with clinical and laboratory improvement, she was discharged with a prescription for prednisone 40 mg/day and was given generic follow-up orientations.

On physical examination in the present case, she had an axillary temperature of 37.9 °C (100.22 °F), oxygen saturation of 96% in room air, blood pressure of 110 x 80 mmHg, slight jaundice and pallor. Fetal heartbeats were present and normal.

Laboratory tests showed hemoglobin of 4.2 g/dl, 13,000 platelets/mm<sup>3</sup>, hematuria, lactate dehydrogenase (LDH) of 2,014 U/l, erythrocyte sedimentation rate (ESR) of 135 mm/h, and C-reactive protein (CRP) of 62.4 mg/l. Prothrombin and activated thromboplastin time were normal. Thus, we ordered the tests summarized in Table 2. This investigation showed presence of anemia with reticulocytosis, schistocytes in blood smears, hypohaptoglobinemia, left-shift leukocytosis, secondary iron overload due to hemolysis and elevation of D-dimer and antiphospholipid antibodies (Table 2).

Red blood cell and platelet transfusions were performed. The hypothesis of TTP or HUS was suggested and we requested an analysis on ADAMTS13 activity. Increasing platelet levels and normalization of hemoglobin were observed, even without specific treatment. The patient was instructed to continue treatments as an outpatient of the nephrology department. Evaluation of

prothrombin and activated thromboplastin time was requested and both of these were normal.

One month after having been discharged, she returned to this hospital complaining of weakness, with swollen face and legs that had developed one day earlier. She was in a good general condition, with presence of normal fetal heartbeats. At this new admission, she had the same laboratory abnormalities, but this time her creatinine was 1.6 mg/dl. A hematological assessment was requested: the results from the ADAMTS13 activity analysis had just been received. The analysis showed that the activity level was less than 5%, without any presence of anti-ADAMTS13 autoantibodies. After this confirmation of the presence of congenital TTP, plasmapheresis was scheduled and plasma infusion was implemented at a dose of 10 ml/kg every 8 hours while waiting for the plasmapheresis.

However, plasmapheresis was delayed because of the high risk of bleeding. During this period, she developed paresthesia in the face and limbs and became fatigued. The fetal heartbeats became inaudible and fetal death was confirmed by means of ultrasound. Delivery was induced using misoprostol, which led to expulsion of the conceptus after 15 hours. Histopathological examination on the fetus showed that it weighed 318 grams and had a gestational age compatible with 16-17 weeks of pregnancy, with a second-trimester hyalinized placenta.

The feasibility of plasmapheresis was confirmed four days after confirmation of the diagnosis and indication of the procedure. Plasma exchange was performed using 16 fresh frozen plasma units, with a good response, and the patient was returned to a plasma infusion regimen two days later. Because she responded to maintenance therapy, we then discharged her for outpatient treatment.

**Table 2.** Laboratory tests ordered on the second day after admission and results

Complete blood count		Other tests	
Erythrocytes	1.5 x 10 <sup>9</sup> cells/mm <sup>3</sup> (4.2-5.2)	ESR*	134 mm/h (< 15)
Hemoglobin	5 g/dl (12-15)	PT/INR*	12"/1.03 (9.5-13.5/0.8-1.2)
Hematocrit	12.6% (37-47)	aPTT*	26" (28-42)
White blood cells	11.6 x 10 <sup>3</sup> cells/mm <sup>3</sup> (5-10)	Bilirubin	0.7 mg/dl (< 1.20)
Metamyelocytes	0% (0)	Creatinine	0.9 mg/l (0.6-1.1)
Band cells	6% (0)	Urea	28 mg/dl (15-40)
Neutrophils	53% (52-72)	LDH*	1,072 UI (200-480)
Lymphocytes	31% (20-30)	CRP*	61.7 mg/l (< 6)
Eosinophils	2% (2-4)	D-dimer	773 FEU/ml (< 500)
Monocytes	8% (4-8)	Fibrinogen	442 mg/dl (160-465)
Platelets	9 x 10 <sup>3</sup> mm <sup>3</sup> (130-450)	Complement C3c	122 mg/dl (83-193)
		Complement C4	20 mg/dl (15-57)
		Reticulocytes	372 x 10 <sup>3</sup> cells/mm <sup>3</sup> (20.5-102)

\*ESR = erythrocyte sedimentation rate; PT/INR = prothrombin time/international normalized ratio; aPTT = activated partial thromboplastin time; LDH = lactate dehydrogenase; CRP = C-reactive protein.

## DISCUSSION

Through descriptions of TTP cases, reviewed in 1966, the clinical pentad formed by anemia, thrombocytopenia, fever and neurological and kidney disorders became the diagnostic criteria for TTP.<sup>10</sup> Nowadays, with the availability of plasmapheresis, only thrombocytopenia and microangiopathic hemolytic anemia are necessary for suspicion of TTP and for implementation of early treatment.<sup>11</sup> After the first case report of TTP associated with pregnancy, subsequent descriptions found the same association, first manifested through gastrointestinal symptoms and then through hypertension closer to term, with serious neurological and renal abnormalities. These cases evolved to death through disseminated intravascular coagulation, in the absence of plasmapheresis.<sup>12</sup> The major features of acquired TTP, congenital TTP and hemolytic uremic syndrome are summarized in **Table 3**.

The incidence of TTP is 1 in 25,000 to 1 in 198,000 pregnancies. The outcome is often unfavorable when it is presented in the second trimester and, without prophylaxis, recurrence in future pregnancies is close to 100%.<sup>4</sup> The main factors contributing to occurrence or recurrence of TTP during pregnancy are a hypercoagulable state and progressive deficiency of ADAMTS13 over the course of gestation.<sup>12</sup> Fibrinogen, factor VIII and von Willebrand factor levels have been found to increase up to threefold during pregnancy.<sup>12,13</sup> The physiological increase in von Willebrand factor concentration seems to be directly related to the decrease in ADAMTS13 activity. Thus, women with congenital ADAMTS13 deficiency may become severely disabled during pregnancy.<sup>12</sup>

Relapses, defined as acute events of TTP occurring 30 days after remission, are seen in 20 to 50% of cases. They are more common in patients with low ADAMTS13 activity or with autoantibodies after remission.<sup>14</sup>

Differentiation between congenital and acquired TTP is needed, through measurement of ADAMTS13 activity and autoantibodies,

since use of immunosuppressive therapy is critical in cases of acquired TTP but is unnecessary in cases of congenital TTP.<sup>8</sup> The largest prospective study on pregnancy-associated TTP evaluated 47 women.<sup>8</sup> Fetal loss occurred in 42% of the congenital TTP cases before the diagnoses, but without further losses in subsequent pregnancies if proper management was instituted. Most cases of TTP occurred in the third trimester, and only 15% of the cases occurred before the 20<sup>th</sup> week. In all pregnancies in which a diagnosis of TTP was made, labor was induced at the 38<sup>th</sup> week, because of the increased risk of complications that is observed in pregnancies that continue to term and beyond. That study concluded that pregnancy is a precipitating factor for TTP; that there is a risk of relapse in further pregnancies; and that, in pregnancies, late-onset congenital TTP occurs more often than acquired TTP. Treatment with plasma therapy and antithrombotic agents in further pregnancies has been found to result in improvement of fetal growth and placental histology, without fetal loss.<sup>8</sup>

A French study assessed 42 women who had had a first episode of TTP during pregnancy or postpartum.<sup>4</sup> The rate of live births was only 31% and was associated with the time of onset of this condition: 96% of those in whom it occurred during the first and second trimester presented abortion or fetal death, compared with 17% among those who had the disease during the third trimester. Only two patients attained remission without plasma therapy, and both of them had congenital TTP.<sup>4</sup>

In the case reported here, the patient had four episodes of TTP: two before pregnancy (at the ages of 9 and 16 years), and two during pregnancy, both in the second trimester of gestation. During the first and third episodes of TTP, spontaneous remission (i.e. without any plasma therapy) was observed and, as far as we know, this is the only case reported in the literature. The diagnoses was suspected at the time of the second hospitalization and, if the ADAMTS13 activity level had been investigated, this would have had a great impact on the patient's life and pregnancy outcome,

**Table 3.** Major features of TTP-HUS<sup>2,3,5</sup>

	Acquired TTP	Congenital TTP	HUS
Cause	Autoantibodies against ADAMTS13.	Homozygous or compound heterozygous ADAMTS13 mutation.	Toxin from the enteric bacteria <i>Escherichia coli</i> or <i>Shigella dysenteriae</i> .
Clinical features	Adult with ischemic organ injury or acute kidney injury; occurrences in children are rare.	Often in a child, but may be in an adult, with possible ischemic organ injury; acute kidney injury is uncommon; heterozygotes are asymptomatic.	Young child with acute kidney injury; can occur sporadically or in outbreaks.
Treatment	PEX and immunosuppression.	Plasma infusion.	Supportive care.
Prognosis	Mortality rate 1% with PEX and 90% without; 20% continue to present sequelae; high risk of relapses.	Unknown; may be better than for acquired TTP	Good; mortality rate and significant sequela rate are 5%; hypertension and neurological deficit may persist; end-stage renal disease is rare.

TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic uremic syndrome; ADAMTS13 = "a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13"; PEX = plasma exchange.

since the diagnosis would have been known and she would probably have had different management.

It can be seen that suspicion of this disease is impaired through persistence of the “classical pentad” concept and the difficulty in characterizing signs and symptoms as part of a single syndrome. The differential diagnoses of microangiopathic hemolytic anemia and thrombocytopenia during pregnancy are summarized in **Table 4**.

The hemoglobinuria seen in our patient’s previous manifestations and the onset of paresthesia during the current case reflect the renal and neurological impairments of the disease that occur in severe cases. The presence of “left shift” leukocytosis, elevated inflammatory markers, leukocyturia and hematuria are often confused with infectious condition,<sup>15</sup> which should always be a differential diagnosis and should be ruled out through cultures.

It is known that systemic infections may mimic TTP.<sup>15</sup> From analysis on 415 consecutive patients in the Oklahoma TTP Registry who were initially diagnosed with TTP, two distinct groups were identified: 25 patients with measured ADAMTS13 activity whose symptoms were later attributed to systemic infections; and 62 patients with ADAMTS13 activity < 10% whose symptoms remained assigned to TTP. In the “systemic infections” group, more cases with fever, coma and the classical TTP pentad were identified, along with more lethal cases. In the TTP group, 31% did not show any neurological abnormalities, but the presence of relapses and focal deficits was higher and the average platelet and hematocrit levels were lower than in the first group. This study revealed that the classical clinical pentad is rare among cases of TTP and is much more common in cases of sepsis. Nevertheless, it still has great influence on many physicians, since there is usually a belief that if more features of the pentad are present, the diagnosis of TTP becomes more likely.<sup>15</sup>

Since no anti-ADAMTS13 autoantibodies are present in cases of congenital TTP, treatment of acute cases by means of plasma exchange or plasma infusion alone is appropriate.<sup>3,5,14</sup> After remission of acute symptoms has been achieved, the treatment should be individualized according each patient’s phenotype. Some patients may require monthly plasma infusions to restore ADAMTS13 and prevent symptomatic episodes, while others only require prophylactic therapy under risky conditions such as surgery,

infections, pregnancies and presentation of thrombocytopenia.<sup>3,5</sup> A study involving four European TTP registries found that low residual ADAMTS13 activity was associated with early manifestations requiring plasma therapy and with higher frequency of recurrences.<sup>16</sup> Since congenital TTP is hereditary, evaluation of ADAMTS13 activity among close relatives should be considered.<sup>14</sup>

Blood transfusions and folic acid supplementation are indicated during hemolysis, especially if there is cardiac impairment.<sup>5,14</sup> However, platelet transfusions are relatively contraindicated and are only acceptable when there is life-threatening bleeding.<sup>5,14</sup> Patients with TTP who receive platelet transfusions have a higher chance of arterial thrombosis (adjusted odds ratio, adjOR = 5.8; 95% confidence interval, CI = 1.3-26.6) and myocardial infarction (adjOR = 2.0; 95% CI = 1.2-3.3), and higher mortality (adjOR = 2.0; 95% CI = 1.3-3.0).<sup>17</sup>

In managing congenital TTP in subsequent pregnancies, low doses of acetylsalicylic acid in association with regular plasma infusion are recommended as soon the pregnancy has been confirmed, starting at a dose of 10 ml/kg every two weeks, and changing to once a week after the 20<sup>th</sup> week.<sup>8</sup> If the patient is thrombocytopenic, the plasma dose may be increased to 15 ml/kg. It is recommended that delivery should take place between the 36<sup>th</sup> and 38<sup>th</sup> week because this has been proven to reduce fetal loss and relapses.<sup>8</sup>

## CONCLUSION

This report reveals the importance of suspicion of TTP in the presence of microangiopathic hemolytic anemia and thrombocytopenia that do not have any apparent cause. Waiting for the classical pentad to appear before making the suspected diagnosis and introducing treatment is unwise and can seal the outcome. Because of the risks involved in plasmapheresis, presence of systemic infection mimicking TTP needs to be ruled out.

To date, the present case provides the only description of congenital TTP with two spontaneous remissions in the literature. Spontaneous remissions may reflect a milder phenotype of TTP. Obtaining clarifications from patients regarding their condition is essential for identifying the factors that may precipitate worsening of disease and for managing possible recurrences.

**Table 4.** Differential diagnoses of microangiopathic anemia and thrombocytopenia during pregnancy<sup>3,8,9,14,15</sup>

Condition	Onset	Characteristic features	Treatment
TTP	Any time	Microangiopathic hemolytic anemia and severe thrombocytopenia; renal, hepatic and neurological abnormalities may not be present; absence of DIC.	Plasma infusion (congenital TTP); plasma exchange (acquired TTP).
Severe preeclampsia and HELLP syndrome	After 20 <sup>th</sup> week	Microangiopathic hemolytic anemia, thrombocytopenia and elevated liver function tests; hypertension; presence of DIC in severe cases; may become indistinguishable from TTP.	Delivery
Systemic infections	Any time	Fever, hypotension, mild anemia (may be microangiopathic) and thrombocytopenia; renal abnormalities are common; positive cultures.	Antibiotics

TTP = thrombotic thrombocytopenic purpura; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver-enzyme levels and low platelets.

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# What do Cochrane systematic reviews say about interventions for vitamin D supplementation?

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## ABSTRACT

**CONTEXT AND OBJECTIVE:** Despite the high prevalence of vitamin D supplementation, its use remains controversial. The objective of this review was to identify and summarize the evidence from Cochrane systematic reviews regarding vitamin D supplementation for preventing or treating any clinical condition.

**DESIGN AND SETTING:** Review of systematic reviews, conducted in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo.

**METHODS:** A search was conducted to identify all Cochrane systematic reviews that fulfilled the inclusion criteria. Titles and abstracts were screened by two authors.

**RESULTS:** We included 27 Cochrane systematic reviews: 10 assessing use of vitamin D for prevention and 17 for treatment. The reviews found moderate to high quality of evidence regarding the benefit of vitamin D for pregnant women (prevention of adverse events: preterm birth risk [rate ratio, RR 0.36; 95% confidence interval, CI 0.14 to 0.93] and low birthweight risk [RR 0.40; 95% CI 0.24 to 0.67]) and for asthma patients (reduction of severe exacerbations [RR 0.63; 95% CI 0.45 to 0.88]). No benefit was found regarding vitamin D supplementation alone (without calcium) for preventing hip or any new fracture. For all other outcomes assessed under various conditions, the current quality of evidence is low or unknown, and therefore insufficient for any recommendation.

**CONCLUSION:** Based on moderate to high quality of evidence, the Cochrane systematic reviews included here showed that there were some benefits from vitamin D supplementation for pregnant women and asthma patients and no benefits for preventing fractures.

## INTRODUCTION

A series of national surveys in the United States<sup>1</sup> have shown that vitamin supplementation is done most commonly in relation to vitamin D. These analyses, relating to 2011-2012, showed that the prevalence of vitamin D supplementation was around 40%. After excluding supplementation using multivitamin or multiminer sources, the frequency of vitamin D supplementation was still high (approximately 19%).<sup>2</sup> In addition, use of vitamin D supplementation has been increasing over the years. Supplementation with this micronutrient (excluding multivitamin/multiminer sources) was around 5.1% in 1999-2000 (with a difference of 14 percentage points from the 2011-2012 prevalence).<sup>2,3</sup> The intake of high-dose vitamin D supplements (more than 1000 IU/day) has also increased. In 1999-2000, a prevalence of 0.3% was reported, versus 15.8% in 2011-2012.<sup>4</sup>

The number of published papers relating to vitamin D has also increased over time. A quick search in MEDLINE (via PubMed), using the strategy (“Vitamin D”[Mesh]) and a broad filter of clinical trials, retrieved 192 references in 2016, versus 75 in 1996 (a mean of 150 references per year was found over the period considered). Despite the popularity of vitamin D use and the high number of studies on this topic, the efficacy and safety of its supplementation are still a matter for debate in the literature.<sup>5</sup> Because of the variety of dosages and formulations for vitamin D supplements and significant clinical heterogeneity between the conditions under which vitamin D is hypothesized to have benefits, the conclusions are still confusing.

Therefore, considering (a) the vast use of vitamin D supplementation, (b) the high number of primary studies published and (c) the controversy that continues in the literature, a systematic synthesis of the available evidence, such as the present review, is essential.

**OBJECTIVE**

To identify and summarize the evidence from Cochrane systematic reviews regarding vitamin D supplementation for preventing or treating any clinical condition.

**METHODS****Design and setting**

A review of Cochrane systematic reviews was conducted within the Discipline of Evidence-based Medicine of Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-Unifesp). This article was specifically developed for the section Cochrane Highlights, which is an initiative for disseminating Cochrane reviews. This initiative results from a formal partnership between the São Paulo Medical Journal and Cochrane, and it is supported by Cochrane Brazil.

**Inclusion criteria***Types of study*

We included any completed Cochrane systematic reviews published in the Cochrane Database of Systematic Reviews (CDSR). Protocols of systematic reviews and withdrawn or outdated versions of systematic reviews were not included. There was no limitation regarding date of publication.

*Types of participants*

Healthy individuals or those diagnosed with any clinical condition were included, regardless of age, ethnicity or sex.

*Types of intervention*

We considered systematic reviews on vitamin D supplementation, in any form (active or non-active), presentation (capsules or oral solution), dose (high, conventional or underdoses), regimen or duration of use, as a single or combined intervention. We did not consider reviews in which the clinical question involved vitamin D in combination with other interventions and in which it was not possible to assess the effect of vitamin D in isolation.

*Types of outcomes*

We considered any clinical or laboratory outcomes evaluated by the authors of the systematic reviews.

**Search for reviews**

We conducted a systematic search in the Cochrane Database of Systematic Reviews (CDSR) (via Wiley) on April 4, 2017, sensitively using the MeSH term "Vitamin D" in titles, abstracts and keywords.

**Selection of reviews**

The titles and abstracts were read by two out of three authors (MVM, RLP or DVP) independently. The systematic reviews that met the inclusion criteria was selected. Any disagreement was solved by consulting a further author (RR or COCL).

**Presentation of results**

The results from the search and the systematic reviews included were presented through a descriptive structure (qualitative synthesis).

**RESULTS****Search results**

Our search strategy retrieved 53 references and, after screening the titles and abstracts, 28 systematic reviews were preselected. After assessing full texts, 27 reviews<sup>6-32</sup> were found to fulfill our inclusion criteria and were included for qualitative analysis. One systematic review that assessed vitamin D plus calcium supplementation for treating corticosteroid-induced osteoporosis was excluded because it was not possible to evaluate the effect of vitamin D in isolation.<sup>33</sup>

**Reviews included**

A summary of the issues, objectives, main findings and quality of evidence among the 27 systematic reviews included is presented below. We also present a brief individual summary of each review included, according to the clinical situation. For detailed explanations, the full versions can be viewed in the box in **Table 1**.<sup>6-32,34</sup>

**1. Asthma**

The review<sup>6</sup> evaluated the effect of vitamin D for preventing asthma attacks or improving disease control, in comparison with placebo or no intervention. Nine randomized clinical trials (RCTs) involving 1,093 participants were included. The majority of the participants were considered to have mild to moderate asthma. The results showed that vitamin D presents benefits relating to:

- Risk of exacerbations requiring systemic corticosteroids (number of events per participant per year, during a follow-up of six to 12 months (rate ratio, RR 0.63; 95% confidence interval, CI 0.45 to 0.88; three RCTs; 680 participants; high-quality evidence);
- Risk of experiencing at least one exacerbation requiring an emergency department visit or hospitalization or both (odds ratio, OR 0.39; 95% CI 0.19 to 0.78; seven RCTs; 963 participants; high-quality evidence).

There was no difference between the intervention groups for the following outcomes: predicted percentage of forced expiratory

**Table 1.** Main characteristics relating to clinical situation, intervention, findings and quality of evidence among the systematic reviews included

Clinical situation	Vitamin D	Findings	Quality of evidence (GRADE approach*)
Asthma <sup>6</sup>	500 IU/day to 4000 IU/day	Reduction of risk of exacerbations requiring systemic corticosteroids and risk of having at least one exacerbation requiring an emergency department visit or hospitalization or both. No difference in predicted percentage of forced expiratory volume in one second, asthma control test scores or risk of serious adverse events.	Moderate to high
Atopic eczema <sup>7</sup>	1000 IU/day to 1600 IU/day	No reliable evidence for benefits or harm.	-
Sickle cell disease <sup>8</sup>	240,000 to 600,000 IU in six weeks	Higher serum vitamin D levels at eight, 16 and 24 weeks.	-
Multiple sclerosis <sup>9</sup>	4,000 IU/day to 40,000 IU/day	No reliable evidence for benefits or harm.	-
Epilepsy <sup>10</sup>	2,000 IU/day	No reliable evidence for benefits or harm.	-
Prevention of fractures in postmenopausal women and older men <sup>11</sup>	Many schemes and formulations of vitamin D. For detailed explanations, see full version.	No statistical difference in prevention of hip fracture or any new fracture (vitamin D alone, without calcium).	High
Prevention of adverse outcomes in pregnancy <sup>12</sup>	200 IU/day to 2000 IU/day 35,000 IU/week 200,000 IU to 600,000 IU in single dose	Reductions in preterm birth and in low birthweight. No difference in preeclampsia, gestational diabetes or adverse events.	Moderate
Chronic painful conditions in adults <sup>13</sup>	1,200 IU/day to 100,000 IU/day 50,000 IU/week 150,000 IU in single dose	No difference in pain relief or pain-related outcomes.	-
Prevention of cancer in adults <sup>14</sup>	300 IU/day to 3333 IU/day	No reduction in cancer occurrence rate. Slightly reduction in all-cause mortality. Slight reduction in cancer mortality favoring vitamin D (only for cholecalciferol form).	Low to moderate
Cystic fibrosis <sup>15</sup>	800 IU/day to 1600 IU/day 250,000 IU in single dose	No difference in overall and respiratory outcomes or in vitamin D deficiency disorders.	-
Prevention of mortality among adults <sup>16</sup>	400 IU/day to 100,000 IU/day 18,000 IU/day to 100,000 IU/day 300,000 IU in single dose	Small reductions in all-cause mortality and in cancer-related mortality. Higher risk of nephrolithiasis in treated group (cholecalciferol).	-
Recovery from hip fracture among elderly people <sup>17</sup>	800 IU/day to 2,000 IU/day 50,000 IU in single dose to 100,000 IU in single dose	No difference in mortality or risk of fall-related injury.	-
Latent autoimmune diabetes (LADA) in adults <sup>18</sup>	Alfacalcidol 0.25 ug/day	No reliable evidence for benefits or harm.	-
Sexual dysfunction among patients with chronic kidney disease <sup>19</sup>	Calcitriol 0.25-1.5 µg/d	No reliable evidence for benefits or harm.	-
Cases of chronic kidney disease not requiring dialysis <sup>20</sup>	4000 IU/day Calcitriol 0.25-1 µg/d Paricalcitol 1-2 µg/day	No difference in mortality or risk of dialysis.	-
Cases of chronic kidney disease requiring dialysis <sup>21</sup>	Many schemes and formulations for vitamin D. For detailed explanations, see full version.	No reliable evidence for benefits or harm.	-
Metabolic bone disease in children with chronic kidney disease <sup>22</sup>	Many schemes and formulations for vitamin D. For detailed explanations, see full version.	No reliable evidence for benefits or harm.	-
Kidney transplant recipients <sup>23</sup>	Many schemes and formulations of vitamin D. For detailed explanations, see full version.	No reliable evidence for benefits or harm.	-
Autosomal dominant polycystic kidney disease <sup>24</sup>	Calcitriol 0.25 to 1 µg/day	No reliable evidence for benefits or harm.	-
Prevention of bone outcomes in healthy children <sup>25</sup>	133 IU/day to 2000 IU/day	No differences in total body bone mineral content, hip bone mineral density, lumbar spine bone mineral density or forearm bone mineral density.	-

Continue...

Table 1. Continuation.

Clinical situation	Vitamin D	Findings	Quality of evidence (GRADE approach*)
Prevention of nutritional rickets in term-born children <sup>26</sup>	400 IU/day	No reduction in the risk of rickets.	-
Prevention of infections in children under five years of age <sup>27</sup>	400 IU/day to 2500 IU/day	No differences in all-cause mortality, cause-specific mortality, risk of pneumonia or risk of diarrhea.	Low to moderate
Children and adults with HIV infection <sup>28</sup>	4,000 IU/day to 7,000 IU/day 100,000 IU in single dose	No difference in mortality among HIV patients with active tuberculosis or in CD4 cell count.	Very low to moderate
Active tuberculosis <sup>29</sup>	200/day to 600 IU/day	No differences in mortality, tuberculosis cure at 6 months or sputum-smear or sputum-culture positivity at 8 weeks.	-
Prevention of falls among stroke victims <sup>30</sup>	Many schemes and formulations for vitamin D. For detailed explanations, see full version.	No differences in risk of falls or in the number of fallers (compared with use of placebo or alendronate).	-
Prevention of falls among elderly people in care facilities and hospitals <sup>31</sup>	Many schemes and formulations for vitamin D. For detailed explanations, see full version.	Reduction in rate of falls. No reduction in the risk of falling.	-
Prevention of falls among elderly people living in the community <sup>32</sup>	800 IU/day to 2000 IU/day	No difference in the risk of falling.	-

\*GRADE<sup>34</sup> (Grading of Recommendations Assessment, Development and Evaluation) is used for assessment of the quality of the body of evidence.

volume in one second (mean difference, MD 0.48; 95% CI -0.93 to 1.89; four RCTs; 387 participants; high-quality evidence); asthma control test scores (MD -0.08; 95% CI -0.70 to 0.54; three RCTs; 713 participants; high-quality evidence); and risk of serious adverse events (OR 1.01; 95% CI 0.54 to 1.89; five RCTs, 879 participants; moderate-quality evidence). These results should be taken carefully and their clinical relevance needs to be assessed by an asthma specialist, preferably supported by cost-effectiveness analysis, before any recommendation for practice is made.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011511.pub2/full>.

## 2. Atopic eczema

The review<sup>7</sup> evaluated dietary supplementation, including vitamin D, for treatment of atopic dermatitis. Among the 11 RCTs included in the full review, two studies (n = 63) evaluated the effects of vitamin D supplementation, and showed that there was no benefit from vitamin D use for primary efficacy outcomes (participant/parent-rated symptoms of atopic eczema, such as pruritus or sleep loss, or reduction in the number of flares or need for other treatments) or secondary efficacy outcomes (overall severity assessed by participants or physicians, quality of life or adverse events). Both studies had limited numbers of participants, overall low methodological quality and short follow-up periods, which precluded any definitive conclusion regarding the effect of vitamin D on atopic dermatitis. Therefore, the authors concluded that the current evidence was insufficient for routinely recommending vitamin D for such clinical situations in practice.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005205.pub3/full>.

## 3. Sickle cell disease

Sickle cell disease is associated with multiple micronutrient deficiencies. The review<sup>8</sup> aimed to investigate the effects of vitamin D supplementation on sickle cell disease and only one RCT (39 participants) was found.

Compared with placebo, the vitamin D group had significantly higher serum vitamin D levels after:

- Eight weeks (MD 29.79; 95% CI 26.63 to 32.95; 37 participants; moderate-quality evidence);
- 16 weeks (MD 12.67; 95% CI 10.43 to 14.90);
- 24 weeks (MD 15.52; 95% CI 13.50 to 17.54).

No statistical significance was found in relation to any other outcome evaluated through this RCT. This study was classified as containing a high risk of attrition bias, because only 25 of the 37 randomized participants (67%) completed the six-month follow-up. The authors concluded that no practical recommendation could be made regarding supplementation of vitamin D among patients with sickle cell disease.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010858.pub2/full>.

## 4. Multiple sclerosis

The review<sup>9</sup> evaluated the effects of vitamin D for multiple sclerosis and included only one small RCT (n = 49; 52-week follow-up), which

compared serial doses of vitamin D versus placebo. The authors reported that there was a reduction in the relapse rate, a higher proportion of relapse-free patients and a reduction in the EDSS score (i.e. the disability score) in the intervention group. However, no numerical data were provided. In addition, the RCT included had a small sample size and significant methodological limitation, and so presented substantial risk of bias. Therefore, the current evidence did not provide any solid conclusion regarding the effects of vitamin D on multiple sclerosis.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008422.pub2/full>.

### 5. Epilepsy

The review<sup>10</sup> assessed the effects of different interventions on epilepsy and included 15 RCTs, but only two of them (n = 274) evaluated the use of vitamin D. However, no data were available regarding freedom from seizures, seizure frequency, quality of life, cognitive function, reduced side effects from antiepileptic drugs or any other outcome considered by the review. The studies had significant methodological limitation and therefore high risk of bias. The authors' conclusion was that no reliable evidence was found to support use of vitamin D among epileptic patients.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004304.pub2/full>.

### 6. Postmenopausal women and older men

The purpose of the review<sup>11</sup> was to determine the effects of vitamin D or related compounds for preventing fractures among postmenopausal women and older men. This review included 53 RCTs (n = 91,791) and the results showed that vitamin D alone was not effective for preventing:

- Hip fracture (RR 1.12; 95% CI 0.98 to 1.29; 11 RCTs; n = 27,693);
- Any new fracture (RR 1.03; 95% CI 0.96 to 1.11; 15 RCTs; n = 28,271).

The authors concluded that with the current evidence, vitamin D alone was unlikely to prevent fractures.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000227.pub4/full>.

### 7. Prevention of adverse outcomes in pregnancy

The aim of the systematic review<sup>12</sup> was to assess the effects of oral supplementation with vitamin D during pregnancy for improving maternal and neonatal outcomes. The review included 15 RCTs (n = 2,833) and it showed that vitamin D supplementation during pregnancy provided benefits regarding the following outcomes:

- Risk of preterm birth (RR 0.36; 95% CI 0.14 to 0.93; three RCTs; n = 477; moderate-quality evidence);
- Risk of low birthweight (RR 0.40; 95% CI 0.24 to 0.67; three RCTs; n = 493; moderate-quality evidence).

There was no statistical difference between the groups regarding the risk of preeclampsia (RR 0.52; 95% CI 0.25 to 1.05; two RCTs; n = 219; low-quality evidence), gestational diabetes (RR 0.43; 95% CI 0.05 to 3.45; two RCTs; n = 219; very low-quality evidence) or adverse effects (RR 0.17; 95% CI 0.01 to 4.06; one RCT; n = 135; low-quality evidence). In the light of these results, the authors concluded that the benefits of vitamin D supplementation as part as routine antenatal care were still unclear and that further studies were needed in order to confirm whether there was any benefit in relation to maternal and neonatal outcomes.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008873.pub3/full>.

### 8. Chronic painful conditions in adults

The review<sup>13</sup> assessed the efficacy and safety of vitamin D supplementation versus placebo or versus active comparators, for adults with chronic painful conditions. Ten RCTs (n = 811), including people with rheumatoid arthritis (four RCTs), knee osteoarthritis (two RCTs), polymyalgia rheumatic (one RCT), "non-specific" musculoskeletal pain (one RCT), "diffuse" musculoskeletal pain (one RCT) and fibromyalgia (one RCT), were included. These studies were very heterogeneous regarding clinical and methodological characteristics, and therefore no quantitative analysis was possible. No statistical difference was demonstrated for any primary outcome (number of participants with 50% pain relief, improvement in overall impression of pain change or any other pain-related outcome). Based on these results, no recommendation for any vitamin D supplementation for chronic painful conditions could be made.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007771.pub3/full>.

### 9. Prevention of cancer in adults

The aim of the review<sup>14</sup> was to assess the effectiveness and safety of vitamin D (cholecalciferol, ergocalciferol, alfalcidol and calcitriol) for preventing cancer, and included 18 RCTs (n = 50,623). The following results were found:

- Risk of cancer: no significant reduction through vitamin D supplementation over a follow-up of 0.5 to seven years (RR 1.00; 95% CI 0.94 to 1.06; 18 RCTs; n = 50,623; moderate-quality evidence);
- All-cause mortality: through vitamin D supplementation over a follow-up of 0.5 to 7 years (RR 0.93; 95% CI 0.88 to 0.98; 15 RCTs; n = 49,866; low-quality evidence);
- Cancer-related mortality: no significant reduction through cholecalciferol (RR 0.88; 95% CI 0.78 to 0.98; four RCTs; n = 44,492; low-quality evidence).

This review did not show any evidence of effects from any presentation of vitamin D in relation to reducing the risk of cancer.

It was found that there was a general need for more studies in order to make any recommendations regarding clinical practice.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007469.pub2/full>.

#### 10. Cystic fibrosis

The review<sup>15</sup> examined the effects of vitamin D supplementation for cystic fibrosis patients, and included six randomized and quasi-randomized controlled studies (n = 239). No improvements in general or respiratory outcomes or in vitamin D deficiency disorders (osteopenia or osteoporosis) were found. The high clinical and methodological heterogeneity between studies precluded meta-analysis. The number of published studies was small and there was currently no evidence of clinical benefit from vitamin D supplementation.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007298.pub4/full>.

#### 11. Prevention of mortality among adults

The objective of the review<sup>16</sup> was to assess the benefits and harm from vitamin D supplementation in relation to preventing mortality. It included 159 RCTs, but only 56 (n = 95,286) reported usable data regarding mortality. The following results were found for the comparisons of cholecalciferol versus placebo or no intervention:

- All-cause mortality: reduction of 6% over a seven-year follow-up [(RR 0.94; 95% CI 0.91 to 0.98; number needed to treat (NNT) = 150; 38 RCTs; n = 75,927; moderate-quality evidence)];
- Cancer-related mortality; reduction of 12% (RR 0.88; 95% CI 0.79 to 0.98; four RCTs; n = 44,492; moderate-quality evidence).

For the comparisons of cholecalciferol plus calcium versus placebo or no treatment, the risk of nephrolithiasis was higher in the treated group (RR 1.07; 95% CI 1.02 to 1.34; four RCTs; n = 42,876). The risk of attrition bias due to the substantial drop-out of participants and the risk of outcome reporting bias regarding mortality weakened the current evidence. Further RCTs with strong methodological and reporting quality would be needed in order to draw any practical conclusion.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007470.pub3/full>.

#### 12. Recovery from hip fracture among elderly people

The aim of the review<sup>17</sup> was to evaluate the effects of nutritional interventions among elderly people who were recovering from hip fractures. It included 24 RCTs, but only four RCTs evaluated vitamin D supplementation. There was no evidence of any effects from vitamin D supplementation regarding any primary or clinical outcomes such as mortality or the risk of fall-related

injury. Currently, there was no evidence that vitamin D had any beneficial effect among older patients who were recovering from hip fractures.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001880.pub6/full>.

#### 13. Latent autoimmune diabetes (LADA) in adults

The review<sup>18</sup> aimed to assess the effects of different interventions relating to latent autoimmune diabetes (LADA), which is a kind of type 1 diabetes with slow progression to insulin dependency. Ten RCTs (n = 1,109) were included, but only one related to vitamin D. This study compared vitamin D plus insulin versus insulin alone and showed that the peptide C levels in the combined group remained steady, but that these levels decreased in the insulin-alone group (368 to 179 pmol/L; P = 0.006) over 12 months of follow-up. The lack of methodologically high-quality studies prevented any practical recommendation regarding the use of vitamin D for treatment of LADA.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006165.pub3/full>.

#### 14. Sexual dysfunction among patients with chronic kidney disease (CKD)

The purpose of the review<sup>19</sup> was to evaluate the benefits and harm of interventions for treating sexual dysfunction among CKD patients. It included 15 RCTs (n = 352 patients), but only one RCT (n = 15) aimed to assess the efficacy of vitamin D. No sound benefits were found among the outcomes reported (endocrine parameter levels) in this study. The small sample size and the high risk of bias attributed to this study prevented any conclusion regarding the use of vitamin D for treating sexual dysfunction among CKD patients.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007747.pub2/full>.

#### 15. Cases of chronic kidney disease (CKD) not requiring dialysis

The objective of the review<sup>20</sup> was to evaluate the efficacy of vitamin D for patients with CKD who were not requiring dialysis. Sixteen RCTs (n = 894) were included. Some analyses showed lower serum parathyroid hormone (PTH) concentration and higher calcium and phosphorus concentration, but no benefits in relation to primary clinical outcomes, such as mortality or risk of dialysis, were found. The authors concluded that there were insufficient data to determine the effect of vitamin D on mortality and relevant clinical outcomes among chronic non-dialytic renal patients.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008175/full>.

#### 16. *Cases of chronic kidney disease (CKD) requiring dialysis*

The review<sup>21</sup> aimed to evaluate the efficacy and safety of vitamin D compounds in CKD patients requiring dialysis. It included 60 RCTs (n = 2,773) that evaluated multiple formulations, routes and schedules for administration of vitamin D compounds. No clinically relevant outcomes favored the intervention group in any comparisons. Some analyses showed decreased serum PTH levels and a tendency towards higher calcium and phosphate concentrations. In the light of the low quality and poor reporting, and considering the marked clinical and methodological heterogeneity of the studies available, no strong practical recommendations could be made.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005633.pub2/full>.

#### 17. *Metabolic bone disease in children with chronic kidney disease (CKD)*

The purpose of the review<sup>22</sup> was to examine the benefits and harm of interventions for prevention and treatment of metabolic bone disease in children with CKD. This review included 18 RCTs (n = 576) and evaluated eight different interventions, most of them including at least one vitamin D preparation. Other than differences in PTH levels between groups in some of these comparisons, no other clinical or primary outcome was improved through vitamin D supplementation. Therefore, no solid recommendation in favor of vitamin D supplementation could be made.

For further details and more information about the comparisons included, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008327.pub2/full>.

#### 18. *Kidney transplant recipients*

The aim of the review<sup>23</sup> was to evaluate the use of interventions for preventing bone disease following kidney transplantation. Twenty-four RCTs (n = 1,299) were included. Studies that assessed use of vitamin D sterols and other interventions such as use of bisphosphonates, calcitonin and other substances were considered. The analysis on vitamin D sterol alone versus placebo or no treatment did not show any reduction in the risk of fractures or other clinical outcomes such as all-cause mortality. Some improvement in bone mineral density (lumbar spine and femoral neck) was reported in one RCT. Because of the lack of studies of high methodological quality assessing the use of vitamin D alone for preventing bone disease, it was difficult to come to any practical conclusion before further studies investigating this question are developed.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005015.pub3/full>.

#### 19. *Autosomal dominant polycystic kidney disease (ADPKD)*

The review<sup>24</sup> evaluated the effects of interventions for preventing progression of ADPKD, in relation to kidney function, kidney endpoints, kidney structure, patient-centered endpoints and the adverse effects of these treatments. This review included 30 studies, but only one RCT (n = 34) evaluated vitamin D supplementation, which was done in comparison with Chinese medicine (herbs). The data were sparse and inconclusive, and the authors were unable to make any solid recommendations.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010294.pub2/full>.

#### 20. *Prevention of bone outcomes in healthy children*

The aim of the review<sup>25</sup> was to determine the effectiveness of vitamin D supplementation for increasing bone mineral density in children. Six RCTs were included (n = 884). No statistically significant differences between the vitamin D and control groups were found in relation to:

- Total body bone mineral content (standard mean difference, SMD 0.1; 95% CI -0.06 to 0.26; 5 RCTs; n = 672; high-quality evidence);
- Hip bone mineral density (SMD 0.06; 95% CI -0.18 to 0.29; 4 RCTs; n = 639; moderate-quality evidence);
- Lumbar spine bone mineral density (SMD 0.15; 95% CI -0.01 to 0.31; 5 RCTs; n = 660);
- Forearm bone mineral density (SMD 0.04; 95% CI -0.36 to 0.45; 3 RCTs; n = 427).

The authors concluded that the results did not support supplementation to improve bone mineral in children.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006944.pub2/full>.

#### 21. *Prevention of nutritional rickets in term-born children*

The review<sup>26</sup> aimed to evaluate the effects of any intervention for prevention of rickets in term-born children. It included three RCTs and one non-randomized clinical trials (n = 1,700). Only three studies evaluated use of vitamin D alone, but in two of these studies there were no occurrences of rickets in either group. One study comparing vitamin D (400 IU per day for 12 months) versus no intervention showed that there was a statistical reduction in the risk of occurrence of rickets (RR 0.04; 95% CI 0 to 0.71; one RCT; n = 676). Even in the light of this result, the authors considered it reasonable to offer vitamin D or calcium

for prevention of rickets to all children up to two years of age. However, they pointed out that further studies would be needed to investigate the effects in higher-risk subgroups and to investigate possible adverse effects.

This recommendation needs to be better evaluated, considering that

1. Only one study contributed towards this conclusion;
2. The evaluation on the risk of bias for this systematic review, published in 2007, did not follow the current standard (i.e. the risk-of-bias table from the Cochrane Collaboration); and
3. No assessment of the quality of the body of the evidence was required by the Cochrane Collaboration at the time when this systematic review was published.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006164.pub2/full>.

## 22. Prevention of infections in children under five years of age

The purpose of the review<sup>27</sup> was to evaluate the role of vitamin D supplementation in preventing infections in children under five years of age. Four RCTs (n = 3,198) were included. No difference between the vitamin D and control groups (placebo or no supplementation) was found in relation to the following outcomes:

- All-cause mortality (mortality due to any cause of death) (RR 1.43; 95% CI 0.54 to 3.74; one RCT; n = 3,046; low-quality evidence);
- Cause-specific mortality (mortality due to pneumonia, tuberculosis, diarrhea or malaria) (RR 1.50; 95% CI 0.42 to 5.30; one RCT; n = 3,046; low-quality evidence);
- Risk of a radiologically confirmed first or only episode of pneumonia (RR 1.06; 95% CI 0.89 to 1.26; two RCTs; n = 3,134; moderate-quality evidence);
- Risk of diarrhea (two RCTs; no numerical data provided).

No study investigating other infectious diseases such as tuberculosis or malaria was found. The authors concluded that the implications of this systematic review were limited because of the low availability of primary studies.

For further details, refer to the original abstract, available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008824.pub2/full>.

## 23. Children and adults with HIV infection

The review<sup>28</sup> aimed to evaluate the efficacy and safety of micronutrient supplementation for reduction of morbidity and mortality among adults and children with HIV infection. Thirty-three RCTs were included, but only five (n = 447) were on vitamin D (alone or in combination with calcium). The results showed that vitamin D did not provide any benefit in relation to the following outcomes:

- Mortality among HIV patients with active tuberculosis (RR 1.15; 95% CI 0.65 to 2.02; one RCT; n = 131; very low-quality evidence);
- CD4 cell count (data from four RCTs, not pooled; n = 288).

The authors concluded that further larger RCTs, with strong methodological quality, using individual supplementation of vitamin D would be needed in order to build a baseline of evidence.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003650.pub4/full>.

## 24. Active tuberculosis

The objective of the review<sup>29</sup> was to assess the effects of oral nutritional supplements among individuals receiving anti-tuberculosis drug therapy to treat active tuberculosis. Eleven RCTs evaluated the effects of vitamin D supplementation. The results showed that vitamin D did not provide any benefit in relation to the following:

- Mortality (RR 0.96; 95% CI 0.81 to 1.12; seven RCTs; n = 2,649);
- Tuberculosis cure at six months (RR 0.99; 95% CI 0.75 to 1.31; one RCT; n = 151);
- Sputum-smear or sputum-culture positivity at eight weeks (RR 0.81; 95% CI 0.54 to 1.20; six RCTs; n = 856).

The authors concluded that there was no reliable evidence that would support vitamin D supplementation among people who were being treated for active tuberculosis.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006086.pub4/full>.

## 25. Prevention of falls among stroke victims

Falls are a common complication after stroke. Around 7% of stroke victims suffer falls in the first week after stroke onset. The objective of the review<sup>30</sup> was to evaluate the effectiveness of interventions for preventing falls among these individuals. It included ten RCTs, but only two were on vitamin D. One RCT (n = 85) compared vitamin D versus placebo among women who had been institutionalized after suffering a stroke, and now presented low serum vitamin D levels. The second RCT compared alfacalcidol versus alendronate among individuals who were hospitalized after stroke. For both studies, there was no statistical difference between the vitamin D and comparison groups regarding the risk of falls and the number of fallers. The authors concluded that these data should be considered provisional until further studies had been developed.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008728.pub2/full>.

## 26. Prevention of falls among elderly people in care facilities and hospitals

The review<sup>31</sup> aimed to evaluate the effectiveness of interventions to reduce falls among elderly people. It included 60 RCTs (43 conducted in healthcare facilities and 17 in hospitals), totaling 60,345 participants. In the healthcare facilities, the vitamin

D group had a lower fall rate, defined as the number of falls per person-year (RR 0.63; 95% CI 0.46 to 0.86; five RCTs;  $n = 4,603$ ), but did not have a lower risk of falling, defined as the number of people falling (i.e. fallers) (RR 0.99; 95% CI 0.9 to 1.08; six RCTs;  $n = 5,186$ ). No measurement of the quality of the body of evidence was reported in this systematic review. The authors concluded that, in care facilities, vitamin D supplementation seemed to be effective in reducing the fall rate.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005465.pub3/full>.

### 27. Prevention of falls among elderly people living in the community

The review<sup>32</sup> aimed to evaluate the effects of interventions to prevent falls among the elderly population. The authors included 159 RCTs, but only 7 were on vitamin D ( $n = 9,324$ ). No benefit from vitamin D regarding the risk of falls was found (RR 0.96; 95% CI 0.89 to 1.03; 13 RCTs;  $n = 26,747$ ). The authors concluded that vitamin D supplementation did not seem to reduce the number of falls.

For further details, refer to the original abstract, available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007146.pub3/full>.

## DISCUSSION

This study included 27 Cochrane systematic reviews: 10 related to prevention and 17 assessed use of vitamin D as a therapeutic option. Among the preventive systematic reviews, five focused on healthy individuals for prevention of death,<sup>16</sup> cancer,<sup>14</sup> and other adverse outcomes.<sup>12,25,27</sup> Despite the considerable number of Cochrane reviews, eight of them did not present any reliable evidence regarding benefits or harm from vitamin D, including reviews on clinical situations in which use of vitamin D is frequently observed in clinical practice, such as in relation to multiple sclerosis<sup>9</sup> and atopic eczema.<sup>7</sup> Thus, in those reviews, the authors were unable to provide recommendations regarding the benefits and risks of vitamin D.

Currently, there are major concerns and inconsistencies regarding vitamin D use in clinical practice. Although its use has been disseminated by the media, and is widespread among healthcare professionals and patients, there are few clinical studies supporting this practice. Moreover, the existing studies present poor methodological quality, thus leading to uncertain results.

It is important to highlight that most of the trials providing the current evidence were methodologically inappropriate due to small sample sizes, insufficient follow-up periods or unclear or inadequate methods for randomization and blinding. Furthermore, there was huge clinical and methodological heterogeneity among clinical trials with the same PICO (P = population, I = intervention,

C = comparison, O = outcomes), which precluded additional quantitative synthesis. All of these features limited the quality of current available evidence for relevant outcomes.

A second point that deserves discussion is that many of the reviews included were planned, conducted or published some years ago, and therefore were based on early versions of the Cochrane Handbook, which were less detailed and complex than the current version (<http://training.cochrane.org/handbook>). As an example, the inclusion criteria and methods for assessing the quality of clinical trials were not refined as they are now. Moreover, Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a new approach that was not yet mandatory for Cochrane reviews. Implementation of the Cochrane Risk of Bias Table, and mandatory use of GRADE and Methodological Expectations of Cochrane Intervention Reviews (MECIR) have contributed towards improving the methodological rigor of Cochrane reviews over the years. Therefore, it is reasonable to assume that older reviews may not present the same quality as recent reviews, which could limit the applicability of findings.

Regarding the implications of these Cochrane reviews for clinical practice, moderate to high-quality evidence of benefit from vitamin D for pregnant women (prevention of maternal and child adverse outcomes) and for asthma patients (reduction of severe exacerbations) was found. Additionally, no benefit from vitamin D supplementation alone (without calcium) for preventing hip fracture or any new fracture was found. For all other benefits or harm, the current quality of evidence was low or unknown, and therefore insufficient for any recommendations.

Regarding the implications of this study for further research, it was found that well-designed and well-conducted randomized clinical trials are essential for assessing the effectiveness and safety of vitamin D for many clinical situations, in which 'off-label use' is already commonly observed in clinical practice. Moreover, a number of core questions need to be addressed, including determining definitions for the following: the normal serum levels of vitamin D; the most appropriate type of vitamin D supplementation; the optimal doses for vitamin D supplementation; the most accurate method for assessing serum vitamin D levels; and the relationship between vitamin D and the risk of diseases.

## CONCLUSION

This study identified 27 Cochrane reviews that provided evidence of quality ranging from unknown to high, in relation to vitamin D supplementation as preventive or therapeutic intervention. Vitamin D was found to present some benefit for pregnant women and asthma patients and no benefit when administered alone (without calcium) for preventing fractures. For all other likely benefit or harm that has been evaluated through Cochrane reviews, the current quality of evidence is low or unknown, and therefore insufficient for any sound conclusion.

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**Where it read:**

“<sup>IV</sup>MD, PhD. Full Professor, Institute of Public Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.”

**It should read:**

“<sup>IV</sup>MD, PhD. Full Professor, Instituto de Saúde Coletiva, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.”

## AIM AND EDITORIAL POLICY

### Indexing and scope

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is now published bimonthly by the Associação Paulista de Medicina. It accepts articles in the fields of clinical health science (internal medicine, gynecology & obstetrics, mental health, surgery, pediatrics, epidemiology and public health). Articles will be accepted in the form of original articles, narrative reviews, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

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Abbreviations must not be used, even those in everyday use. Drugs or medications must be referred to using their generic names, avoiding casual mention of commercial or brand names. All drugs should be followed by the dosage and posology used. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses.

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Authors of articles published in São Paulo Medical Journal should all have contributed actively to the discussion of the study results and should review and approve the final version to be released. The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, São Paulo Medical Journal considers that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text.

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The title page must contain:

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The second page must include the title and a 250-word abstract in English (case reports with 100 words). Do not cite references in the abstract.

Use the following headings:

1. Background: Describe the rationale for the study including the research question or the scientific hypothesis.
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- Number the pages.

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### Original articles

Clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis, are considered to be full-text original articles, with a maximum of 3000 words.

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles.

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion). The abstracts in short communications should not be structured and have a maximum of 100 words.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement<sup>5,6</sup>
2. Clinical trials: CONSORT Statement<sup>2</sup>
3. Accuracy studies on diagnostic tests: STARD Statement<sup>8,9</sup>
4. Systematic reviews of the literature and meta-analyses: PRISMA<sup>4</sup>
5. Case reports: CARE<sup>7</sup>

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials have only been accepted for publication if they have received an identification number from one of the clinical trial registers (the options are stated at <http://www.icmje.org>). The identification number should be declared at the end of the abstract. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

### Short communications, case reports, case series and narrative reviews

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion), a maximum of five references and one figure or table. They should be structured in the same way as original articles. Individual case reports should contain the following sections: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.<sup>5</sup>

Both short communications and case reports must be submitted with abstracts and keywords. The abstracts in short communications should not be structured and have a maximum of 100 words.

The São Paulo Medical Journal is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.<sup>11</sup> The search strategy for each database and the number of articles obtained from each database must be shown in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms are appropriate to be utilized for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. Emtree terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT) the search dates should be indicated in the text or in the table.

Narrative reviews may be accepted by the São Paulo Medical Journal provided that a systematic search is made, and they should be structured as Original Articles. The search strategy and results should be presented as described above for case reports. By invitation from the Editor-in-Chief, narrative reviews addressing historical personal or collective experiences relating to clinical health sciences, epidemiology and public health may be accepted, but with no more than two authors.

Individual case reports should contain Introduction, Case Report, Discussion and Conclusion. Case reports should be structured in accordance with the norms of the CARE Statements.<sup>7</sup> Case reports published in São Paulo Medical Journal must be submitted with abstracts and keywords.

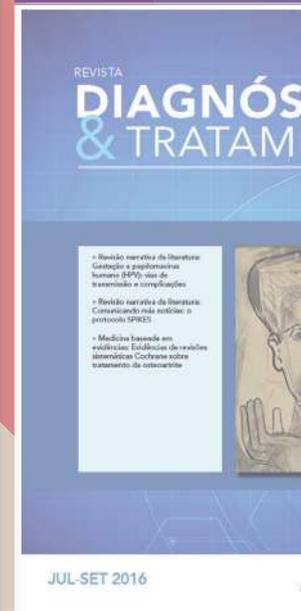
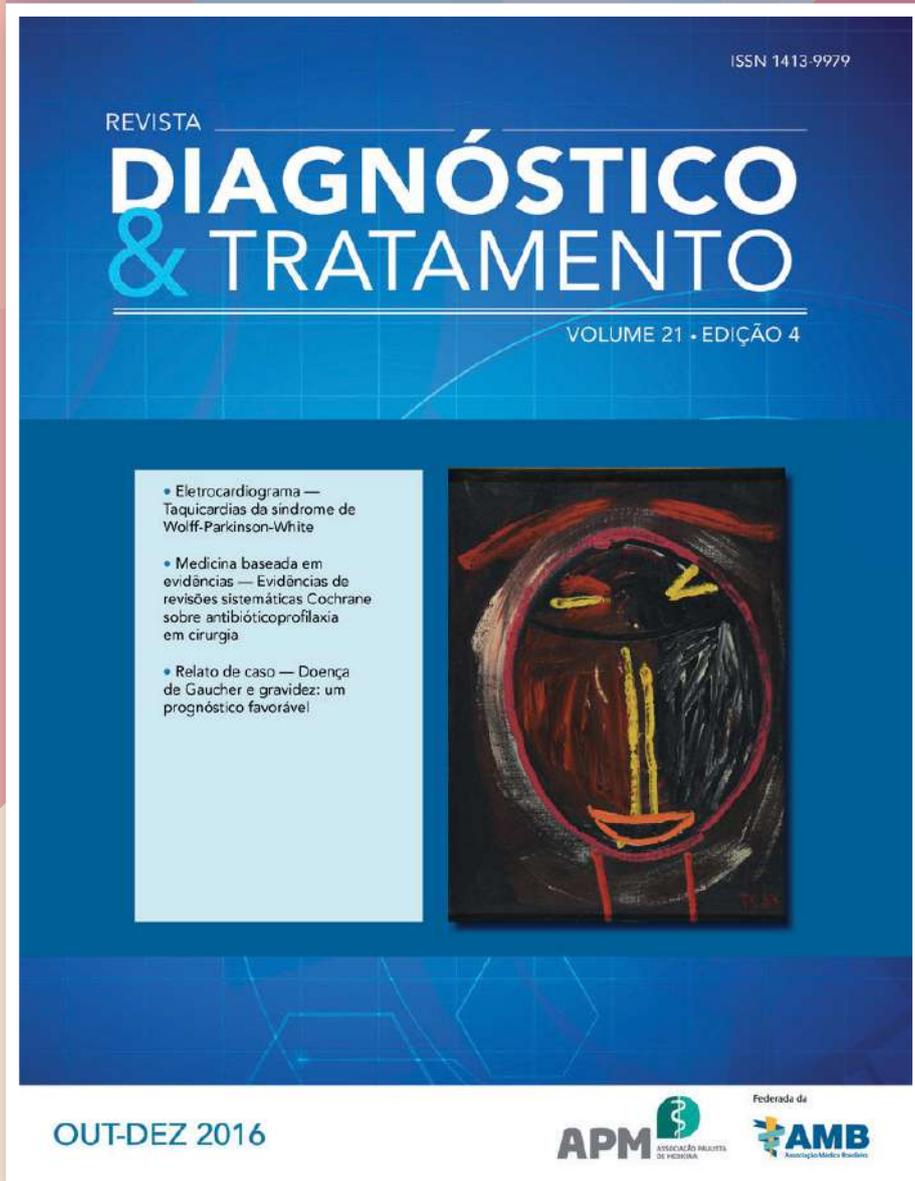
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# Água, luz e plano de saúde de qualidade: não dá para ficar sem.

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1R\$ 217,35 - Exato Adesão Trad. 16 F AHO QC COP (registro na ANS nº 476.942/16-2), da SulAmérica Saúde, faixa etária até 18 anos, com coparticipação e acomodação coletiva (tabela de julho/2017 - SP). Planos de saúde coletivos por adesão, conforme as regras da ANS. Informações resumidas. A comercialização dos planos respeita a área de abrangência das respectivas operadoras de saúde. Os preços e as redes estão sujeitos a alterações, por parte das respectivas operadoras de saúde, respeitadas as disposições contratuais e legais (Lei nº 9.656/98). Condições contratuais disponíveis para análise. Outubro/2017.

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