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### Translation and validation study:

- Translation to Brazilian Portuguese, cultural adaptation and reproducibility of the questionnaire "Ankylosing Spondylitis: What do you know?"

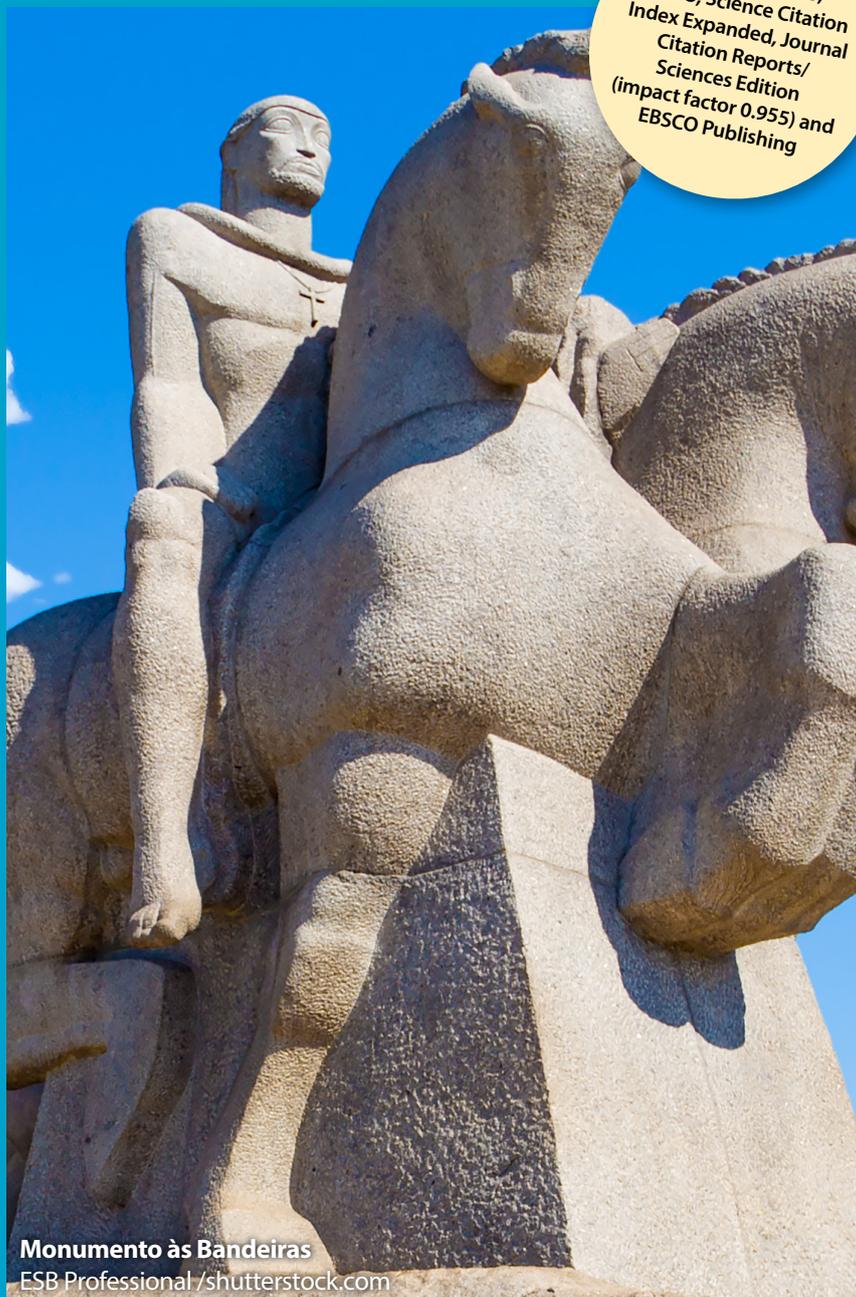
### Cross-sectional study

- Stages of hyperglycemia and common mental disorders in adults – The Brazilian Study of Adult Health (ELSA-Brasil)

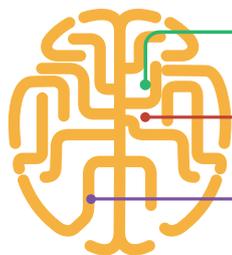
### Ecological study:

- Trends in mortality from ill-defined causes among the elderly in Brazil, 1979-2013

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# From screening-driven medicine to symptom-driven medicine

## Da medicina guiada por triagem para a medicina guiada por sintomas

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Each year, there are celebrations of the breast cancer and prostate cancer awareness months, respectively during October and November. In addition to being fundraising movements, these very well-orchestrated worldwide movements have blurred any public health planning for prevention and treatment of other diseases and conditions, except for AIDS. Cancer and AIDS activists do not have limits on obtaining more money and funds. They are the materialization, within medical and public affairs in the 2010s, of the European trade unionist ideology of the second half of the 19<sup>th</sup> century and the first quarter of the 20<sup>th</sup> century, when a refrain of “more, more and more” was celebrated.<sup>1</sup> One undisputable fact is that the propaganda has been successfully reaching lay people. For example, a survey conducted in São Paulo revealed that the population investigated considered that cancer and AIDS were the most important causes of deaths.<sup>2</sup> However, perusal of the files of the official health statistics for Brazil in 2014 shows that this is not true. In fact, the risk of premature mortality (< 70 years of age) due to breast cancer is almost a quarter of the risk due to stroke; and the rates of prostate cancer are a fifth of those of heart disease.\*<sup>3</sup>

If, on the one hand, the medical-industrial complex relating to cardiovascular diseases has enough power to equilibrate this dispute, on the other hand, health conditions with little or no support exist. These conditions relate to the burden of morbidity with low lethality rates.

The current issue of the Journal presents original articles addressing low-back pain,<sup>3,4</sup> frailty,<sup>5-7</sup> ankylosis spondylitis<sup>8</sup> and knee osteoarthritis.<sup>9</sup> The constant decline in age-adjusted mortality rates for all causes including chronic diseases, combined with the increasing size of the elderly population, is bringing up a new agenda for medical and public health research.<sup>10</sup> This agenda relates not only to avoidance of lethal diseases, but also to reduction of discomfort and painful conditions.<sup>11</sup>

Current demographic and epidemiological profiles are demanding greater focus on research on the epidemiology of conditions such as low-back and neck pain, frailty, osteoarthritis, migraine, hearing loss, refractive and accommodation errors of vision, depression and anxiety. These conditions are not unique to Brazil, and they are among the top ten leading causes of years lived with disability, according to the Global Burden of Diseases, 2013.<sup>11</sup>

**Table 1** shows the top ten conditions that cause years lived with disability (YLD) globally, in developed and developing countries and in Brazil. In decreasing order, the top ten significant illnesses associated with years lived with disability in Brazil are low-back pain, major depressive disorder, anxiety, diabetes, hearing loss, other musculoskeletal conditions, asthma, neck pain, migraine and chronic pulmonary obstructive disease.<sup>11</sup>

One condition that deserves particular comment is low-back pain. The 2013 Brazilian National Health Survey investigated people over 18 years of age and found that 18.5% of the interviewees reported having some type of complaint relating to the lumbar column. The frequency was higher in urban areas than in rural areas, among women and among people with lower education, and it was age-related, with a plateau at around 27% after 60 years of age.<sup>12,13</sup> Although the magnitude of lumbar pain is extremely relevant, the quality of the studies conducted so far has been insufficient, such that they lack internal and external validity to support preventive measures.<sup>14</sup>

\*Available from: [www.datasus.gov.br](http://www.datasus.gov.br).

**Table 1.** The top ten causes of years lived with disability (YLD) according to the Global Burden of Diseases, 2013

	Global	Developed countries	Developing countries	Brazil
1	Back pain	Back pain	Back pain	Back pain
2	Major depression	Major depression	Major depression	Major depression
3	Iron deficiency	Neck pain	Iron deficiency	Anxiety
4	Neck pain	Other musculoskeletal conditions	Neck pain	Diabetes
5	Hearing	Hearing	Hearing	Hearing loss
6	Migraine	Diabetes	Migraine	Other musculoskeletal conditions
7	Diabetes	Migraine	Diabetes	Asthma
8	Chronic obstructive pulmonary disease	Falls	Chronic obstructive pulmonary disease	Neck pain
9	Anxiety	Anxiety	Anxiety	Migraine
10	Other musculoskeletal conditions	Chronic obstructive pulmonary disease	Other musculoskeletal conditions	Chronic obstructive pulmonary disease

Clinical care for osteoarticular complaints, psychiatric diseases, migraine and respiratory disorders needs to have greater presence on the agenda relating to public health. These are conditions that deserve more attention with regard to identifying risk factors and testing new therapies to relieve symptoms. Unfortunately, we are wasting time and money during the breast and prostate cancer awareness months.

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# Bipedal locomotion, spinal pain and psychiatric disorders. Is this our future?

Locomoç o b pede, dores na coluna e dist rbios psiqui tricos.   este o nosso futuro?

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Bipedal locomotion is probably the oldest and one of the most important characteristics of humans. The process of evolution that led to bipedalism is poorly understood, with several knowledge gaps. Is it possible that spinal pain is a consequence of this adaptive process that began a long time ago? Why would this be so important now?

The Global Burden of Disease study 2013 (GBD 2013) published a list of the more common causes of disability-adjusted life-years (DALYs) at three points of time: 1990, 2005 and 2013. DALYs may be understood, in a simple way, as the lost years of “healthy” life.<sup>1</sup> They are calculated as the sum of the years of life lost (YLL) due to premature mortality in the population and the years lost due to disability (YLD) for people living with an adverse health condition or its consequences. Low-back pain was the seventh biggest cause of DALYs in the world in 1990, the fifth in 2005 and the fourth in 2013. Only three diseases cause more DALYs than low-back pain, according to GBD 2013: ischemic heart disease, stroke and lower respiratory infections.<sup>1</sup> The situation in Brazil is that low-back pain is the first of YLD and the second biggest cause of DALYs, just behind coronary heart disease (CHD), and followed by violence, stroke, road accidents, diabetes, depression, anxiety, chronic obstructive pulmonary disease and sensory losses.<sup>1</sup>

In this issue of S o Paulo Medical Journal, an article is published<sup>2</sup> that estimates the prevalence of chronic spinal pain in individuals aged 15 years or over, in a sample from a region of the city covered by the Family Health Program. The study also compared quality of life among individuals with and without chronic spinal pain. Chronic spinal pain encompasses neck pain, upper back pain and low-back pain.

What is the importance of this article? It is very simple: if low-back pain is the second biggest cause of DALYs in Brazil, it is time to know more about this symptom and factors associated with it. In the sample, the most important associated factors were sex (women), age, education (low educational attainment), occupational history (physical work) and anxiety symptoms. Psychiatric disorders are a very important cause of chronification of any pain process. The associated factors reported in the analysis published in this issue of the journal are similar to those in previously published studies that showed that psychiatric disorders were common factors associated with low-back pain.<sup>3</sup>

GBD 2013 showed that depressive disorders were the 15<sup>th</sup> biggest cause of DALYs in 1990, the 14<sup>th</sup> in 2005 and the 11<sup>th</sup> in 2013.<sup>1</sup> In Brazil, depression and anxiety disorders are respectively the seventh and eighth biggest cause of DALYs in our population, according to GBD 2013. Low-back pain, depression and anxiety disorders do not occupy stable positions in the list of the most frequent causes of DALYs. At each new measurement, they have been rising through the rankings. Therefore, we need to be prepared for further ascension over the coming years.

Few studies in Brazil have addressed spinal pain. In a previous systematic review on the prevalence of back pain in Brazil conducted in 2015, it was concluded that there were no representative studies with the capacity to depict the generalizable prevalence of low-back pain in Brazil. The small number of studies available that were included in this review showed a high risk of bias.<sup>4</sup> Another study published in 2013 calculated the number of years with which individuals lived with low-back pain, using data from the Brazilian Household Sample Survey

(PNAD). The results showed that men born in Brazil in 2008 will have a life expectancy of 69.2 years, of which 15% will be spent with chronic spinal diseases; while women born in the same year will have a life expectancy of 76.7 years and can expect to live a fifth of their lives with chronic spinal diseases.<sup>5</sup>

The study published in this issue of the journal not only fills this gap but also brings insights towards better understanding of the burden of spinal pain in Brazil.<sup>2</sup> Has the price of bipedalism now become inflated? Or are we now more worried about quality of life as a new step towards health? Independent of what the right answer is, this is now the moment to raise a red flag signaling the need for public health policies directed towards adaptation of healthcare services to the increasing frequency of spinal pain and especially low-back pain over the coming years.

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# Towards a unified and standardized definition of the frailty phenotype

Rumo a uma definição unificada e padronizada do fenótipo de fragilidade

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Frailty among older adults has been associated with several adverse health outcomes, including falls, hospitalization, functional decline and death.<sup>1</sup> Although the prevalence of frailty is increasing, with high morbidity and mortality among older adults, systematic description of the frailty phenotype is recent.<sup>2</sup> In 2001, Fried et al. defined frailty as a clinical syndrome that is present if three or more of the following criteria are present:<sup>1</sup> unintentional weight loss of 4.5 kg over the past year, self-reported exhaustion, weakness (measured via grip strength), slow walking speed and low physical activity. The cutoffs for weakness, slowness and low physical activity were defined as the lowest 20<sup>th</sup> percentile in the Cardiovascular Health Study.<sup>2</sup>

Despite current advances in defining frailty, significant confusion remains, mainly because of multiple definitions for frailty and lack of standardized measurements. In addition to Fried's definition of the frailty phenotype, other definitions have been proposed. The Frailty Index was developed using data from the Canadian Study of Health and Aging and took into consideration the number of deficits over time (i.e. disability, diseases, physical and cognitive impairments, psychosocial risk factors and geriatric syndromes).<sup>3</sup> Another popular definition came from the Study of Osteoporotic Fractures (SOF Index), which defined frailty based on the presence of weight loss, inability to rise from a chair without using arms and reduced energy level.<sup>4</sup>

In this issue of the Sao Paulo Medical Journal, two papers address the frailty syndrome using different samples from Brazil. Tavares et al. investigated the association between frailty and cardiovascular risk factors in 205 patients at a tertiary-level hospital.<sup>5</sup> Using Fried's definition of frailty, 26% of the sample were frail, 52% were pre-frail and only 22% were non-frail. The cutoffs for weakness and slowness were based on the original description of Fried et al.<sup>2</sup> In addition, Tavares et al. used the International Physical Activity Questionnaire (IPAQ) to measure physical activity level, while this was defined in accordance with the Minnesota Leisure Time Activities Questionnaire in the original study by Fried et al.<sup>2</sup> In the study by Tavares et al., the only cardiovascular risk factor associated with frailty was overweight, which was more prevalent among pre-frail patients.

The other paper, which is also published in this issue of the São Paulo Medical Journal, used a sample of community-dwelling older adults who were living in Ribeirão Preto, Brazil (Study of Frailty in Elderly Brazilian Individuals, FIBRA).<sup>6</sup> Calado et al. found a prevalence of only 9% for frailty, 50% for pre-frailty and 41% non-frailty. The authors used the same criteria as described by Fried et al.,<sup>2</sup> but they used specific cutoff points for weakness, slowness and low physical activity that were calculated based on the distribution of these variables in the FIBRA study. In addition, they used the Minnesota Leisure Time Activities Questionnaire to measure physical activity, following the original description by Fried et al.<sup>2</sup> Calado et al.<sup>6</sup> found baseline associations of frailty with stroke, diabetes, neoplasia, osteoporosis, urinary and fecal incontinence, more medical visits and hospitalizations.

The striking differences in frailty prevalence and related risk factors were probably due to the different characteristics of the samples, given that Tavares et al. used inpatients at a tertiary-level hospital and Calado et al. used community-dwelling older adults. However,

the differences in the criteria used to define frailty should also be taken into consideration, as pointed out above. In fact, in a systematic review, the prevalence of frailty among community-dwelling older adults was found to vary enormously, ranging from 4 to 59%.<sup>7</sup> According to the authors of this review, differences in putting the frailty phenotype into practice were the main reason for the wide differences in prevalence among the studies. Further attempts should be made to unify and standardize the definitions of frailty in order to have a well-defined intervention that could be clearly targeted in clinical randomized trials, with the aim of decreasing the adverse health outcomes relating to frailty.

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# Prevalence of chronic spinal pain and identification of associated factors in a sample of the population of São Paulo, Brazil: cross-sectional study

Prevalência de dores de coluna crônicas e identificação de fatores associados em uma amostra da população da cidade de São Paulo, Brasil: estudo transversal

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## KEY WORDS:

Back pain.  
Chronic pain.  
Low back pain.  
Prevalence.  
Cross-sectional studies.

## PALAVRAS-CHAVE:

Dor nas costas.  
Dor crônica.  
Lombalgia.  
Prevalência.  
Estudos transversais.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Chronic spinal pain, especially low-back pain and neck pain, is a leading cause of years of life with disability. The aim of the present study was to estimate the prevalence of chronic spinal pain among individuals aged 15 years or older and to identify the factors associated with it.

**DESIGN AND SETTING:** Cross-sectional epidemiological study on a sample of the population of the city of São Paulo.

**METHOD:** Participants were selected using random probabilistic sampling and data were collected via face-to-face interviews. The Hospital Anxiety and Depression Scale (HADS), EuroQol-5D, Alcohol Use Disorders Identification Test (AUDIT), Fagerström test for nicotine dependence and Brazilian economic classification criteria were used.

**RESULTS:** A total of 826 participants were interviewed. The estimated prevalence of chronic spinal pain was 22% (95% confidence interval, CI: 19.3-25.0%). The factors independently associated with chronic spinal pain were: female sex, age 30 years or older, schooling level of four years or less, symptoms compatible with anxiety and high physical exertion during the main occupation. Quality of life and self-rated health scores were significantly worse among individuals with chronic spinal pain.

**CONCLUSION:** The prevalence of chronic spinal pain in this segment of the population of São Paulo was 22.0%. The factors independently associated with chronic pain were: female sex, age 30 years or older, low education, symptoms compatible with anxiety and physical exertion during the main occupation.

## RESUMO

**CONTEXTO E OBJETIVO:** A dor de coluna crônica, especialmente dor lombar e cervical, é uma causa importante de anos de vida com incapacidade. O objetivo deste estudo foi estimar a prevalência de algias vertebrais crônicas em indivíduos com 15 ou mais anos de idade e identificar fatores associados.

**TIPO DE ESTUDO E LOCAL:** Estudo epidemiológico de corte transversal em uma amostra da população da cidade de São Paulo

**MÉTODO:** A seleção de participantes foi feita por amostragem probabilística aleatória e a colheita de dados, por entrevistas presenciais. Foram utilizadas a escala hospitalar de ansiedade e depressão (HADS), o EuroQol-5D, o teste de identificação de desordens devido ao uso de álcool (AUDIT), o teste de Fagerström para dependência de nicotina e o critério de classificação econômica Brasil.

**RESULTADOS:** Um total de 826 participantes foi entrevistado. A prevalência de algias vertebrais crônicas foi estimada em 22% (intervalo de confiança, IC 95%: 19,3-25,0). Os fatores independentemente associados com algias vertebrais crônicas foram: sexo feminino, 30 ou mais anos de idade, quatro anos ou menos de escolaridade, sintomas compatíveis com ansiedade e esforço intenso físico durante a ocupação principal. Participantes com algias vertebrais crônicas apresentaram escores de qualidade de vida e auto-avaliação de saúde significativamente piores.

**CONCLUSÃO:** A prevalência de algias vertebrais crônicas em um segmento da população de São Paulo foi de 22%. Os fatores independentemente associados à dor crônica foram: sexo feminino, idade igual ou superior a 30 anos, baixa escolaridade, sintomas compatíveis com ansiedade e esforço físico durante a ocupação principal.

## INTRODUCTION

Spinal pain is one of the most commonly reported musculoskeletal conditions.<sup>1</sup> It has been estimated that 5-10% of cases of spinal pain become chronic<sup>2,3</sup> and one fifth lead to pain-related disability one year after the first pain episode.<sup>4</sup> Low-back pain and neck pain are the biggest and fourth biggest causes of years of life with disability worldwide, respectively, and the prevalence of neck pain is surpassed only by major depressive disorder and other musculoskeletal disorders.<sup>5</sup>

The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists past the normal time of tissue healing. For nonmalignant pain, three months has been suggested as the most convenient point of division between acute and chronic pain. Chronic pain is a complex syndrome that involves biological, cognitive and lifestyle components.<sup>6,7</sup> The American College of Rheumatology classification criteria for fibromyalgia define chronic widespread pain (CWP) as pain in the left and right sides of the body, above and below the waistline, together with axial skeletal pain.<sup>8</sup>

Reviews of the literature on chronic pain have indicated that the prevalences of chronic neck pain, upper back pain and low-back pain range from 14.5% to 51%,<sup>9-15</sup> 10% to 20%<sup>11,12,16</sup> and 15% to 45%,<sup>1</sup> respectively. In Brazil, one study reported that the prevalence of chronic spinal pain (CSP) was 19%,<sup>17</sup> and three other Brazilian studies reported prevalences of low-back pain ranging from 4.0 to 14.7%.<sup>18-20</sup>

Cultural and socioeconomic differences and distinct criteria for classifying chronic pain have been described as factors affecting the prevalence estimates for chronic pain.<sup>21,22</sup> Several studies have used the duration of pain as the sole definition of chronic pain, and while most studies have defined chronic pain as pain that lasts for three months,<sup>9,11,12,14,23,24</sup> others have considered it to be pain that persists for six or more months.<sup>10,20,25</sup> Some studies have also included additional criteria for CSP, such as the presence of pain episodes over the last month and a score greater than or equal to 5 on a 0-10 visual analogue pain scale.<sup>25,26</sup>

Chronic spinal pain, especially low-back and neck pain, is usually associated with other painful conditions<sup>27,28</sup> and psychological disorders.<sup>3,29</sup> Female sex, greater age, low education levels, low socioeconomic status, anxiety and depression are commonly associated with CSP.<sup>14,18,19,20,23</sup>

Chronic spinal pain is a common symptom within the community and is associated with a significant impact on health. Understanding the epidemiology and impact of CSP is essential in developing public policies aimed towards prevention of spinal pain and health promotion.<sup>30</sup>

## OBJECTIVE

In this study, we estimated the prevalence of CSP among individuals aged 15 years or older and identified the factors associated

with it. We also compared the health-related quality of life of individuals with and without CSP and estimated the prevalence of CWP among individuals with CSP.

## METHOD

This was a cross-sectional epidemiological study conducted in the central-western area of the city of São Paulo, Brazil, which is covered by the Family Health Program (FHP). The study was approved by the Research Ethics Committee of the University of São Paulo Medical School, the Research Ethics Committee of the São Paulo Municipal Health Department and the Research Ethics Committee of the Hospital Irmandade da Santa Casa de Misericórdia de São Paulo, which manages the “Dr. Alexandre Vranjac” Teaching Healthcare Center in Barra Funda, São Paulo. Permission to use the EuroQol-5D instrument was granted by the EuroQol group. All families residing in the study area were registered at this healthcare center.

## Population and sample

The community consisted of 8,052 individuals grouped into 2,549 families. Households were divided into 17 geographically defined micro-areas, each consisting of approximately 150 households. For this study, the prevalence of chronic spinal pain was estimated at 16%, based on a recent study conducted at a primary healthcare unit in São Paulo.<sup>31</sup> The sample size was estimated as 482 individuals, considering a sampling error of 3% and a 95% confidence interval, but was then raised by 30% due to the expected losses, to a total of 627 individuals. Data collection for this study was conducted in conjunction with another study that evaluated the prevalence of chronic pain.<sup>32</sup> Thus, 820 individuals were to be interviewed.

Participants were selected using a probability sampling method. In each micro-area, a number of households proportional to the size of the micro-area was selected using the random number generator function in the Excel software, version 2010.11. The Kish method was used to select one individual aged 15 years or older within each household. This method uses a pre-assigned table for each household, in which all residents are listed based on age and sex, relative to the head of the household. The member within the household to be interviewed is previously selected from the table to which the household has been assigned.<sup>33</sup>

Individuals of both sexes aged 15 years or older and registered with the FHP at the Barra Funda Healthcare Center were eligible to participate. Those who were unable to answer the questions during the interview, for whatever reasons, were not included in the study. Each household was visited up to four times, at different hours of the day and on different days of the week, in order to maximize the chance of contact with the selected participant. When the selected participant could not be reached after four visits, a person from another household was selected, using the

same method described above. Re-draws were made to replace selected participants who were not interviewed.

A large number of foreigners from Bolivia, Paraguay and South Korea were found to be residing in the study area. Because of the language barrier and their reluctance to participate in the interview owing to their likely irregular status in the country, this group of individuals was excluded from the study.

### Data collection and instruments

Home interviews were conducted by two authors and by previously trained undergraduate students. A pilot study was conducted at a university practice ambulatory clinic to train interviewers and potentially improve the questionnaire.

In accordance with the criteria from the International Association of Pain, chronic pain was defined as persistent pain for three or more months.<sup>6</sup> In order to avoid selecting participants with low-frequency chronic pain, participants needed to report at least one pain episode in the previous month. Respondents with chronic pain were asked to indicate all their painful regions, by marking them on a diagram representing the front and back views of a human figure. We used a modified version of the Brief Pain Inventory, which originally divided the human body into 45 regions.<sup>34</sup> In our study, the diagram was divided into 59 regions (Figure 1).

Respondents were asked to indicate the main location of pain, i.e. the area that hurt the most, by marking the diagram in Figure 1 with an arrow. Individuals with CSP were defined as those who indicated areas corresponding to the cervical, thoracic or lumbar regions, whether or not those were the main sites of pain.

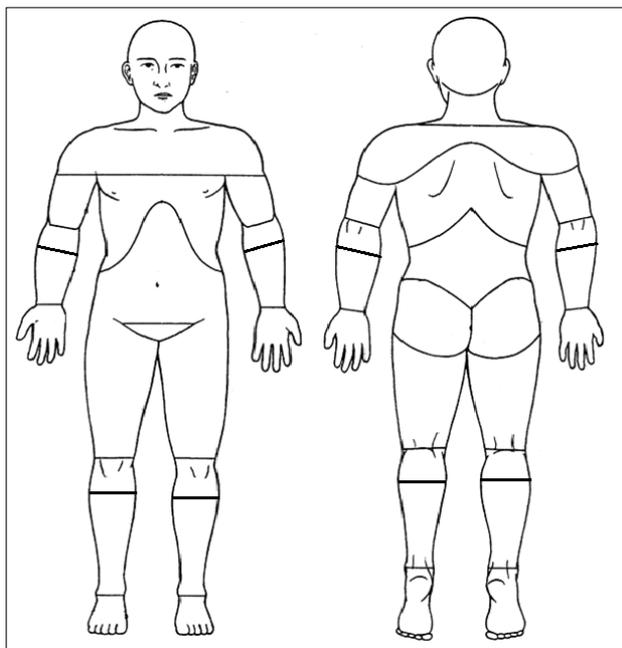


Figure 1. Pain diagram.

Low-back pain was defined as pain localized in the region bounded by the twelfth rib, superiorly; the gluteal line, inferiorly; and the anterior axillary line, anteriorly. Neck pain was defined as pain localized in the region bounded by the lower edge of the occipital bone, superiorly; the spine of the scapula, inferiorly; and the anterior edge of the sternocleidomastoid muscle, anteriorly. Upper back pain was defined as pain in the posterior part of the chest between the first thoracic vertebrae and the upper contour of the trapezius muscle, superiorly; the twelfth thoracic vertebrae and the lower edge of the twelfth ribs, inferiorly; and the right and left axillary line, laterally.<sup>35</sup>

Chronic widespread pain (CWP) was defined as pain in the left and right side of the body, above and below the waistline. Axial skeletal pain was defined as pain in any of the following regions: neck, anterior or posterior part of the chest, or lower back<sup>8</sup>. Participants with chronic pain who did not have CWP were classified as having chronic regional pain (CRP).

The interview included questions asking for personal and sociodemographic information and administration of a pain questionnaire. Information on the presence of comorbidities was obtained through self-reporting. Additionally, four health assessment scales that had previously been validated and culturally adapted to the Brazilian cultural context, and one socioeconomic status scale, were applied.

Symptoms consistent with anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).<sup>36</sup> HADS was developed to assess non-psychiatric patients in different populations and has 14 items, seven of which relate to anxiety and seven to depression.<sup>37,38</sup> Each item on the questionnaire was scored from 0 to 3 for a maximum score of 21 for either anxiety or depression. In our study, a cutoff of 9/21 points was established for symptoms of either anxiety or depression.<sup>37</sup>

Health-related quality of life was assessed by means of the EuroQol-5D (EQ-5D) instrument. EQ-5D includes questions about the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The final score (EQ-index) combines the five dimensions and ranges from 0 (worst quality of life) to one (best quality of life). In addition, the respondent's self-rated health is recorded on a visual analogue scale (VAS) numbered from 0 to 100, where 100 means the 'best imaginable health state' and 0 means the 'worst imaginable health state'.<sup>39</sup>

The Fagerström Test for Nicotine Dependence (FTND) was used to assess the severity of nicotine dependence. This instrument contains six questions and respondents are assigned to one of five dependence levels.<sup>40,41</sup>

Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT). AUDIT consists of 10 questions: three about hazardous alcohol use, three about dependence symptoms and four about harmful alcohol use. The final scores are grouped into four levels of risk.<sup>42</sup>

The participants' socioeconomic status was assessed by means of the Brazilian Economic Classification Criteria (CCEB), which classify the population into five socioeconomic categories from A to E, based on ownership of a range of durable assets and the head-of-household's education level.<sup>43</sup>

The participants answered all of these questionnaires, except the FTND, which was answered by smokers only.

### Statistical analysis

Descriptive analyses on the median, mean, standard deviation and percentage were used to establish the demographic and clinical characteristics of the sample. The CSP prevalence and its 95% confidence interval (CI) were determined. The association between CSP and the selected variables was estimated using prevalence ratios and their 95% CI.

We used a Cox regression model with constant time and robust variance.<sup>44</sup> Cox regression is commonly used to analyze time-to-event data. When a constant risk period (time = 1) is assigned to all subjects, the hazard ratio estimated by Cox regression equals the prevalence ratio in cross-sectional studies.<sup>45</sup>

In bivariate analyses, statistical associations were determined by means of the log-rank test. For ordinal variables, we used the chi-square test for trend. Variables with a P-value < 0.20 in bivariate analyses were selected for multivariate analysis. Multivariate models were constructed by adding variables one at a time through forward stepwise addition, starting from the variable with the lowest P-value, followed by the other variables with P < 0.20. Variables with a P-value < 0.05 according to the maximum likelihood ratio test were retained in the final model. Lastly, we estimated the PR and 95% CI for each variable in the final model. Data were considered significant at P < 0.05.

The analyses were performed using the STATA 13.0 software (StataCorp LP, College Station, Texas, USA).

## RESULTS

### Characteristics of the source population and response rate

A total of 6,297 individuals aged 15 years or older were included, and most of them (3,666; 58.2%) were women. A total of 1,385 households (54.3% of the registered families) were selected to participate in the study, and one person from each household was selected for the interview. Of the selected individuals, 559 were not interviewed for the following reasons: they were ineligible (n = 277), were not located (n = 220), declined participation in the interview (n = 60) or were deemed dangerous to be interviewed (n = 2). The ineligible individuals were considered thus because they had moved (n = 192), were foreigners (n = 64), were incapable of answering (n = 15), or had died (n = 6). Thus, approximately three quarters of all the eligible individuals selected were interviewed (n

= 826; 74.5%). Re-draws were made to replace all the eligible participants who had not been interviewed.

### Characteristics of the sample

In total, 826 individuals were interviewed between December 2011 and February 2012. The respondents' mean age was  $51.4 \pm 19.3$  years. Most respondents were women (69.0%), single (62.2%) and had completed eight or more years of education (55.2%). Nearly half (48.9%) of the respondents reported suffering from at least one illness, 50.8% were employed at the time of the interview and most (93.7%) reported performing no hard physical activity during the workday. The vast majority of the respondents were of socioeconomic levels B or C (86%) (Table 1).

Symptoms consistent with anxiety and depression were observed in 189 (22.9%) and 96 (11.6%) respondents, respectively. Only 2.2% (14/637) of the individuals without anxiety symptoms had depression, whereas 43.4% (82/189) of the respondents with anxiety symptoms had depression. Most respondents were non-smokers (81.1%) and only 7.6% had high or very high nicotine dependence. Possible alcohol dependence, harmful use of alcohol or hazardous drinking was observed in 8.5% of the respondents (Table 1).

### Prevalence and characteristics of chronic back pain

Chronic spinal pain, defined as persistent pain in the cervical, thoracic or lumbar spine lasting three or more months and at least one pain episode in the last month, was reported by 182 individuals, corresponding to a prevalence of 22.0% (95% CI: 19.3-25.0%). The prevalence of CSP was significantly higher among women (25.8%; 95% CI: 22.2-29.6%) than among men (13.7%; 95% CI: 9.7-18.5; P < 0.001). Chronic low-back pain was reported by 152 individuals, corresponding to a prevalence of 18.4% (95% CI: 15.8-21.2%). Additionally, upper back pain and neck pain were reported by 56 and 47 individuals, respectively, corresponding to prevalences of 6.8% (95% CI: 5.2-8.7%) and 5.7% (95% CI: 4.2-7.5%), respectively. The sum of individuals with cervical, thoracic or lumbar pain exceeded the number of individuals with CSP because 54 respondents reported pain in more than one area (Figure 2). The individuals with CSP indicated  $7.3 \pm 7.2$  painful regions and the mean duration of pain was  $6.6 \pm 8.6$  years (median: 4.0 years.).

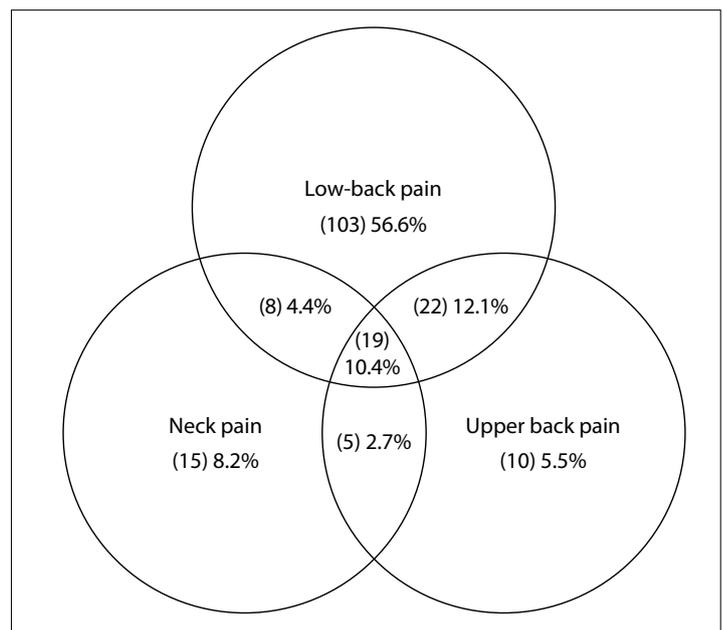
The prevalences of CRP and CWP among the individuals with CSP were 16.7% (95% CI: 14.2-19.3%) and 5.3% (95% CI: 3.8-6.9%), respectively. More than three quarters of the respondents with CSP had CRP (75.8%) and approximately one quarter had CWP (24.2%).

Mean EQ-5D scores were significantly lower among individuals with CSP ( $0.74 \pm 0.2$ ) than among individuals without CSP ( $0.87 \pm 0.17$ ; P < 0.001). Similarly, self-rated health scores were

**Table 1.** Characteristics of the sample

Variable	n	%
<b>Sex</b>		
Male	256	31.0
Female	570	69.0
<b>Age (years)</b>		
15-29	130	15.8
30-59	391	47.3
≥ 60	305	36.9
<b>Marital status</b>		
Single	301	36.4
Married/cohabiting	312	37.8
Divorced/widowed	213	25.8
<b>Education (years)</b>		
0-4	208	25.2
5-8	162	19.6
9-11	298	36.1
12-14	44	5.3
≥ 15	114	13.8
<b>Occupational status</b>		
Currently employed	420	50.8
Retired	176	21.3
Household duties	137	16.6
Unemployed	55	6.7
Student	28	3.4
Away from work	10	1.2
<b>Occupational physical activity</b>		
Sitting or driving or most of the time standing or walking	788	95.4
Frequent weight-bearing or heavy or intense physical activity	38	4.6
<b>Number of comorbidities</b>		
0	400	48.4
1	228	27.6
2	124	15.0
≥ 3	74	9.0
<b>Symptoms consistent with depression</b>		
No	730	88.4
Yes	96	11.6
<b>Symptoms consistent with anxiety</b>		
No	637	77.1
Yes	189	22.9
<b>Current smoking</b>		
No	670	81.1
Yes	156	18.9
<b>Alcohol use</b>		
Low risk	756	91.5
Dependence symptoms, hazardous or harmful use	70	8.5
<b>Socioeconomic level*</b>		
A	27	3.3
B	312	38.0
C	394	48.0
D	75	9.1
E	13	1.6

\*5 individuals without data.

**Figure 2.** Prevalence of chronic spinal pain according to location.

significantly lower among individuals with CSP ( $65.2 \pm 21.5$ ) than among individuals without CSP ( $78.8 \pm 18.8$ ;  $P < 0.001$ ).

#### Factors associated with chronic back pain

The following variables were selected for bivariate analysis: sex, number of comorbidities, symptoms consistent with anxiety, education, symptoms consistent with depression, age, smoking and occupational physical activity (Table 2).

Occupational physical activity was dichotomized in the multivariate analysis to increase its statistical power. In the final model, sex, age, education, anxiety symptoms and occupational physical activity were independently associated with CSP. The prevalence of CSP was higher among women, individuals aged 30 years or older, individuals who had low education, those who had anxiety symptoms and those who reported performing hard physical activity during the workday (Table 3).

#### DISCUSSION

##### Prevalence and characteristics of chronic back pain

This study found that the estimated prevalence of chronic spinal pain was 22.0% (95% CI: 19.3-25.0%) in a sample of the population of São Paulo, Brazil. The separate prevalence estimates for low-back pain, upper back pain and neck pain were 18.4, 6.8 and 5.7%, respectively. Five factors were independently associated with CSP: female sex, age  $\geq 30$  years, education  $\leq 4$  years, anxiety symptoms and regular weight-bearing or heavy or intense physical activity during the workday. The prevalences of chronic regional pain (CRP) and chronic widespread pain (CWP) among individuals

**Table 2.** Univariate analysis on the association between chronic spinal pain and associated factors

Variable	Total	Chronic back pain n (prevalence)	PR	95% CI	P-value
<b>Sex</b>					< 0.001
Male	256	35 (13.7)	1		
Female	570	147 (25.8)	1.89	1.35-2.65	
<b>Age (years)</b>					0.005*
15-29	130	11 (8.5)	1		
30-59	391	98 (25.1)	2.96	1.64-5.35	
≥ 60	305	73 (23.9)	2.83	1.55-5.15	
<b>Marital status</b>					0.454
Single	301	61 (20.3)	1		
Married/cohabiting	312	68 (21.8)	1.08	0.79-1.46	
Divorced/widowed	213	53 (24.9)	1.23	0.89-1.7	
<b>Education (years of schooling)</b>					0.003
> 4	618	121 (19.6)	1		
≤ 4	208	61 (29.3)	1.50	1.15-1.95	
<b>Occupational status</b>					0.237
Student	28	1 (3.6)	1		
Employed	420	91 (21.7)	6.07	0.88-41.98	
Household duties	137	36 (26.3)	7.36	1.05-51.52	
Unemployed	55	10 (18.2)	5.09	0.68-37.84	
Away from work/retired	186	44 (23.7)	6.62	0.95-46.23	
<b>Occupational physical activity</b>					0.047
Sitting or driving or most of the time standing or walking	788	169 (21.5)	1		
Frequent weight-bearing or heavy or intense physical activity	38	13 (34.2)	1.60	1.01-2.53	
<b>Number of (known) comorbidities</b>					< 0.001*
0	400	69 (17.3)	1		
1	228	47 (20.6)	1.20	0.86-1.67	
2	124	31 (25.0)	1.45	1.00-2.10	
≥ 3	74	35 (47.3)	2.74	1.99-3.79	
<b>Symptoms consistent with depression</b>					0.003
No	730	150 (20.6)	1		
Yes	96	32 (33.3)	1.62	1.18-2.23	
<b>Symptoms consistent with anxiety</b>					< 0.001
No	637	111 (17.4)	1		
Yes	189	71 (37.6)	2.16	1.68-2.77	
<b>Current smoking</b>					0.031
No	670	137 (20.5)	1		
Yes	156	45 (28.9)	1.41	1.06-1.88	
<b>Alcohol use</b>					0.672
Low risk	756	168 (22.2)	1		
Dependence symptoms, hazardous or harmful use	70	14 (20.0)	0.90	0.55-1.47	
<b>Brazilian Economic Classification Criteria<sup>†</sup> (classes)</b>					0.219
A	27	4 (14.8)	1		
B	312	64 (20.5)	1.38	0.55-3.51	
C	394	89 (22.6)	1.52	0.61-3.84	
D	75	17 (22.7)	1.53	0.56-4.15	
E	13	6 (46.2)	3.12	1.06-9.16	

\* $\chi^2$  for trend; <sup>†</sup>5 individuals without data. PR = prevalence ratio; CI = confidence interval.

with CSP were 16.7% and 5.3%, respectively. In addition, self-rated quality of life and health were significantly worse among individuals with CSP than among individuals without CSP.

Most epidemiological studies have investigated the prevalence of neck pain, upper back pain, or low-back pain separately,

and few studies have estimated the prevalence of chronic pain in the entire spine. Comparisons of epidemiological data on the prevalence of chronic pain in the cervical, thoracic and lumbar regions may be hindered by the lack of studies that consider the spine as a functional unit.<sup>46</sup>

**Table 3.** Prevalence ratios for variables independently associated with chronic spinal pain through the Cox multivariate regression model with robust variance estimation

Variable	PR <sub>cr</sub>	PR <sub>adj</sub> (95% CI)	P-value
<b>Sex</b>			0.001
Male	1	1	
Female	1.89	1.79 (1.28-2.5)	
<b>Age (years)</b>			0.03*
15-29	1	1	
30-59	2.96	2.89 (1.6-5.2)	
≥ 60	2.83	2.44 (1.33-4.47)	
<b>Symptoms consistent with anxiety</b>			< 0.001
No	1	1	
Yes	2.16	1.99 (1.55-2.54)	
<b>Education (years of schooling)</b>			0.039
> 4	1	1	
≤ 4	1.50	1.32 (1.01-1.71)	
<b>Physical exertion level of current occupation</b>			0.006
Sitting or driving or most of the time, standing or walking	1	1	
Frequent weight-bearing or heavy or intense physical activity	1.60	1.36 (1.09-1.69)	

PR<sub>cr</sub> = crude prevalence ratio; PR<sub>adj</sub> = adjusted prevalence ratio; CI = confidence interval. \* $\chi^2$  for trend.

The estimated prevalence of CSP found in this study was similar to that reported by a recent study conducted in Brazil, which found a prevalence of 19%.<sup>17</sup> To our knowledge, no other Brazilian studies have examined the prevalence of chronic pain in the spine, considering the lumbar, thoracic and cervical spine as a single functional unit. The prevalence of chronic pain reported in our study for different spinal regions was similar to that reported in epidemiological surveys that categorized CSP into low-back pain, neck pain and upper back pain.<sup>1,11,12,16</sup>

The mean duration of pain of  $6.6 \pm 8.6$  years was similar to the duration reported by other epidemiological surveys on the prevalence of chronic neck pain or low-back pain, which also indicated pain of long duration.<sup>47-49</sup> The prevalence of CWP among individuals with CSP in this study (5.3%; 95% CI: 3.8-6.9%) was slightly lower than the values reported by other studies on the prevalence of chronic pain in the general population, in which the prevalence estimates for CWP have ranged from 10-13%.<sup>50,51</sup> A recent study on the prevalence of widespread pain among female primary healthcare patients reported that 28% of women with chronic low-back pain had CWP,<sup>52</sup> higher than the prevalence of CWP among individuals with CSP in the present study.

### Multivariate analysis

Female sex was independently associated with CSP. This finding is consistent with several epidemiological surveys on the prevalence

of back pain and chronic pain.<sup>14,17-19,46,48,53-55</sup> The greater prevalence of pain among women than among men may be related to cognitive and social factors. Moreover, the higher prevalence of pain among women may be a result of reporting bias, given that several studies have suggested that women are more likely to report pain than men.<sup>56</sup>

The prevalence of CSP was higher among individuals aged 30 years or older and was lower in the 60+ age group than in the 30 to 59-year age group. Several studies have reported that there is greater prevalence of chronic pain with increasing age.<sup>8,10-15</sup> An increase in the prevalence of CSP with age has been attributed to several factors, including the increased number of comorbidities and the presence of age-related changes in the musculoskeletal system.<sup>57,58</sup> Conversely, some studies have reported a slight reduction in the prevalence of low-back and neck pain after the seventh decade of life.<sup>18,59</sup> The reasons for this decline of pain remain unclear, but it is possibly related to reporting bias, because back pain may be perceived as a natural part of growing older, as other age-related diseases become apparent, thus leading to underreporting of pain.<sup>60</sup>

Four years of education or less was independently associated with CSP. Conversely, we did not find any association between socioeconomic status and CSP. Two epidemiological surveys conducted in Brazil found that chronic pain was associated with education level, but not with socioeconomic status.<sup>6,61</sup> Several studies have found an association of general chronic pain, and CSP in particular, with low education.<sup>8,10-15,18-20,23</sup> On the other hand, others have shown that less educated people are more likely to be affected by disabling back pain.<sup>62,63</sup>

Symptoms of anxiety and depression were positively associated with CSP. However, only anxiety symptoms remained independently associated with CSP in the multivariate model. The prevalence of symptoms consistent with anxiety (22.9%) or depression (11.6%) among individuals with CSP in our study was comparatively higher than estimates from other studies on chronic spinal pain. A multicenter study on mental disorders among individuals with chronic back or neck pain reported prevalences of depression and anxiety ranging from 2.5 to 15.7% and from 0.5 to 8.7%, respectively.<sup>64</sup> Unlike in our study, an association between chronic pain and depression has been reported more frequently than an association between chronic pain and other emotional disorders, including anxiety.<sup>64</sup>

Intense physical activity or frequent weight-bearing during the workday were independently associated with CSP. Similar findings have been reported for low-back pain.<sup>10,18,65</sup> Eriksen et al.<sup>10</sup> reported that individuals with jobs that required intense physical effort and frequent weight-bearing activities were more likely to be affected by chronic pain than those with a sedentary occupation (OR: 2.2; 95% CI: 1.6-3.1). Conversely, other

studies have suggested that mechanical factors such as lifting and carrying do not play a major role in the pathophysiology of back pain.<sup>66</sup>

### Study limitations

The limitations of the current study need to be noted. Firstly, the cross-sectional design cannot be used to infer a causal relationship between the factors studied and back pain. The sample size was estimated to calculate the prevalence of CSP and therefore it might not have been sufficient to identify associated factors. Secondly, because we sampled individuals from a specific region of São Paulo, it may not be possible to directly extrapolate our results to the entire population of the city. Additionally, the proportion of female respondents (69.0%) was higher than the proportion of women in the source population (58.2%). A higher proportion of women than of men has often been observed in population-based studies on chronic pain<sup>16,54,61,67,68</sup> and back pain,<sup>46,13,16-18</sup> which may lead to overestimation of the prevalence of pain. In our study, the higher proportion of women in the sample can be explained by the fact that 59% of the source population consisted of women. Moreover, most households were composed of one or two members only, and 69% of the members of these households were women. Thus, when a selected man was not interviewed, he was more likely to be replaced by a woman in a subsequent draw.

The strengths of the current study should also be noted. We used a rigorous method for participant selection. Our use of a sample from a population registered with a healthcare unit enabled us to gain access to sociodemographic information for proper planning of data collection. Telephone and letter-based interviews are the two most common types of interview used in epidemiological surveys on the prevalence of back pain, whereas home interviews are rarely used.<sup>15,18,20</sup> Our use of home interviews may have improved the reliability of data collection. For each household, we were careful to make home visits at different times of the day and on different days of the week, including weekends, in an attempt to meet with participants who worked. The repeated visits resulted in a relatively high response rate (74.5%) for eligible individuals. Our use of five validated health-related quality of life instruments (depression, anxiety, alcohol use, smoking, quality of life and socioeconomic status) provided reliable data on the factors associated with CSP.

### CONCLUSION

This was the first epidemiological study to estimate the prevalence of chronic spinal pain in the largest city in Latin America. The prevalence of CSP in our sample was 22.0%. The factors independently associated with the outcome variable were female sex, age 30 years and older, low education level, anxiety

symptoms and high occupational physical activity. Our suggestions for future research include a more detailed investigation of subgroups of people with chronic spinal pain, in order to identify those who are more likely to develop more severe conditions or who have greater demand for healthcare services.

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# Frailty syndrome in an independent urban population in Brazil (FIBRA study): a cross-sectional populational study

Síndrome da fragilidade em uma população urbana independente no Brasil (estudo FIBRA): um estudo transversal populacional

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## KEY WORDS:

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## PALAVRAS-CHAVE:

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Fatores socioeconômicos.  
Morbidade.  
Estudos transversais.  
População urbana.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Frailty is a multifactorial syndrome. The aim of this study was to determine the prevalence and characteristics of frailty syndrome in an elderly urban population.

**DESIGN AND SETTING:** Cross-sectional study carried out at the homes of a randomized sample representing the independent elderly individuals of Ribeirão Preto, Brazil.

**METHODS:** Sociodemographic characteristics, clinical data and criteria of the frailty phenotype were obtained at the subjects' homes; 385 individuals were evaluated. Frailty was defined based on detection of weight loss, exhaustion, weakness, slowness and low physical activity level. Individuals with three or more of these characteristics were classified as frail and those with one or two as pre-frail. Specific cutoff points for weakness, slowness and low physical activity level were calculated.

**RESULTS:** The participants' mean age was  $73.9 \pm 6.5$  years, and 64.7% were women. 12.5% had lost weight over the last year; 20.5% showed exhaustion, 17.1% slowness, 24.4% low physical activity level and 20.5% weakness. 9.1% were considered frail and 49.6% pre-frail. Frail subjects were older, attended more medical visits, had a higher chance of hospitalization within the last 12 months and had more cerebrovascular events, diabetes, neoplasms, osteoporosis and urinary and fecal incontinence.

**CONCLUSION:** In this independent elderly population, there were numerous frail and pre-frail individuals. Frailty syndrome was associated with high morbidity. Cutoff points for weakness, slowness and low physical activity level should be adjusted for the population under study. It is essential to identify frail and pre-frail older individuals for appropriate interventions.

## RESUMO

**CONTEXTO E OBJETIVO:** Fragilidade é uma síndrome multifatorial. O objetivo deste estudo foi determinar a prevalência e características da síndrome da fragilidade em uma população urbana de idosos.

**TIPO DE ESTUDO E LOCAL:** Estudo transversal realizado nas casas em amostra randomizada para representar os idosos independentes de Ribeirão Preto, Brasil.

**MÉTODO:** Características sociodemográficas, dados clínicos e critérios do fenótipo da fragilidade foram obtidos nas casas. Foram avaliados 385 idosos. A definição da fragilidade foi baseada na detecção de perda de peso, exaustão, fraqueza, lentidão e baixo nível de atividade física. Idosos com três ou mais destas características foram classificados com frágeis; com uma ou duas características como pré-frágeis. Foram calculados pontos de corte específicos para fraqueza, lentidão e baixo nível de atividade física.

**RESULTADOS:** A média de idade dos participantes foi de  $73,9 \pm 6,5$  anos, com 64,7% de mulheres. 12,5% perderam peso no último ano, 20,5% tiveram exaustão, 17,1% lentidão, 24,5% baixo nível de atividade física e 20,5% fraqueza. Foram considerados frágeis 9,1% e pré-frágeis 49,6%. Os frágeis eram mais velhos, foram em mais consultas médicas, tiveram maior chance de internação nos últimos 12 meses e tiveram mais eventos cerebrovasculares, diabetes, neoplasias, osteoporose, incontinência fecal e urinária.

**CONCLUSÃO:** Em uma população idosa independente, existem vários indivíduos frágeis e pré-frágeis. A síndrome da fragilidade foi associada com alta morbidade. Pontos de corte para fraqueza, lentidão e baixo nível de atividade física devem ser ajustados para a população em estudo. É essencial identificar idosos frágeis e pré-frágeis para intervenções apropriadas.

## INTRODUCTION

Frailty is a clinical multifactorial syndrome involving reduction of the functional reserves and dysfunction of various organic systems. It results in marked reduction of the ability to reestablish functions after aggression of various natures.<sup>1</sup>

Based on this multifactorial concept, Fried et al. proposed that a phenotype with five components should be envisaged: weight loss, exhaustion, weakness, slowness and low physical activity.<sup>2</sup> Individuals with three or more of these characteristics would be classified as frail and those with one or two characteristics as pre-frail. According to Fried et al., older individuals who meet these criteria are more susceptible to falls, functional decline, recurrent hospitalization and death within three years.<sup>2</sup> These criteria are the ones most frequently used by investigators in epidemiological and clinical studies.<sup>3-5</sup>

The incidence and prevalence of frailty syndrome vary and are influenced by the geographic location studied, by socioeconomic factors such as education, and by age, such that its incidence and prevalence are higher among individuals aged 80 years or over.<sup>2,3,6-10</sup>

Studies conducted both in Brazil and in other countries have reported different prevalence rates, ranging from 6.9% to 40.6% among frail elderly individuals and 46.3% to 60.1% among pre-frail individuals.<sup>2,4,11-14</sup> In this regard, frailty syndrome should be targeted by earlier investigations and interventions, given its impact on elderly individuals, their families and society as a whole.<sup>1</sup> Despite recent initiatives, there are few Brazilian studies assessing this condition, and interventions that reduce the impact of this syndrome are still insufficient.<sup>15</sup>

## OBJECTIVE

The aims of this study were to determine the prevalence and sociodemographic and clinical profiles of frailty syndrome in an independent elderly urban Brazilian population, and to calculate specific cutoff points for weakness, slowness and low physical activity for populations similar to the one studied here. These parameters are influenced by anthropometric data and they are reflected in the prevalence of frailty syndrome.

## METHODS

### Setting and participants

A population-based epidemiological cross-sectional study, forming part of the multicenter "Study of Frailty in Elderly Brazilian Individuals" (FIBRA), was conducted in Ribeirão Preto, state of São Paulo, Brazil. This city has approximately 600,000 inhabitants, 8.7% of them over 65 years of age (Brazilian Institute for Geography and Statistics).

The inclusion criteria were that the subjects needed to be aged 65 years or over and living in a randomly selected house.

The sample was obtained in a random manner from area conglomerates and its size was calculated by estimating the proportion of frailty (i.e. the value at which the sample size obtained would be the maximum possible:  $P = 0.50$ ;  $q = 0.50$ ), according to the older population of the city. The significance level was set at 5% ( $\alpha = 5\%$ ;  $Z = 1.96$ ). The sample size was established as 385 volunteers for a sampling error of 5%.

The exclusion criteria comprised presence of severe cognitive deficit suggestive of dementia after evaluation by the Mini Mental State Examination (MMSE); situations of being bedridden or needing to use a wheelchair; presence of sequelae from a stroke with localized loss of strength; greater age with presentation of end-stage disease; or situations of undergoing treatment for cancer, except for skin cancer.

In order to obtain a representative sample of the elderly population of Ribeirão Preto, we calculated the proportion of older individuals in each neighborhood in relation to the total number of older individuals in the city, on the basis of data from the Brazilian Institute for Geography and Statistics. We then calculated the density of elderly people per household in each neighborhood. The city blocks in which households were visited were identified and selected randomly using maps supplied by the Brazilian Institute for Geography and Statistics and by the city's administration. If the home was inhabited by more than one elderly individual, all of them were invited to participate. Situations in which the elderly individuals categorically stated that they did not want to participate or that they wanted to discontinue participation, after starting, were considered to be refusals. When an elderly individual was present and interested in participating, but declared that he or she was unable to do so at that moment, or a resident or neighbor said that an elderly person lived in the house but was not present at that moment, the interviewer scheduled a new visit, orally and in writing, up to a total of three attempts. If the house was closed on the occasion of the first visit by the interviewer, and it was not possible to know whether an elderly individual lived there, this was considered to be a loss of data. Refusal did not involve exclusion of the home from the total count because the sample calculation had taken the possibility of this occurrence into consideration.

An additional proportional number of city blocks was selected in each neighborhood in order to cover for absences and to replace losses due to the exclusion criteria of the study. The elderly individuals were invited to participate through personal contact at their homes.

### Measurements

A standard assessment tool was formulated and first tested in a pilot study in order to check for any failures and to obtain improvements during the formulation process. The pilot study

was conducted in Ribeirão Preto in 2008/2009. It involved undergraduate and postgraduate students at the Ribeirão Preto Medical School and Ribeirão Preto College of Nursing, University of São Paulo, and recruited volunteers. All of this investigative team received prior training at four meetings. Kits containing a tape measure, scale, caliper, a dynamometer for measuring hand-grip strength and markers for the walking test were acquired for applying the protocol after the pilot study had been concluded.

In the standard questionnaire, the subjects were asked to self-report any chronic diseases that had been recognized by a doctor during the past year, and also to state the number of visits to doctors and admissions to hospital that they had had, also during the past year.

The frailty criteria adopted in the present study were based on the clinical syndrome described and defined by Fried et al.<sup>2</sup> Their definition originated within the context of cardiovascular health studies and women's health and aging studies. The group proposed that a frailty phenotype with five components should be envisaged, defined operationally as described below. These criteria have now become established and are widely used in studies on frailty.

1. Weight loss: report of a loss  $\geq 4.5$  kg or  $\geq 5\%$  of body weight during the previous year.
2. Exhaustion: assessed through a self-report of fatigue in response to two questions on the Center for Epidemiological Studies Depression Scale (CES-D). When a subject stated that on three or more days of the week he felt he had to make much more effort to carry out his usual tasks and could not continue them, he received scores for fatigue.
3. Weakness: mean of three measurements with a hydraulic dynamometer (JAMAR Model J00105) on the dominant hand, adjusted for sex and body mass index (BMI). Subjects were considered to be positive when their handgrip strength was below the 20<sup>th</sup> percentile for this population.<sup>2</sup>
4. Low physical activity level: measured from the weekly energy expenditure in kilocalories, with adjustment for sex, based on self-reported activities and physical exercise, and assessed using the Minnesota Leisure Time Activities Questionnaire, which has been validated in Brazil.<sup>16</sup> Subjects in the lowest quartile were considered to be positive for this criterion.<sup>2</sup>
5. Slowness: measured from the time, in seconds, taken to walk 4.6 m and adjusted for sex and height. This criterion was positive for the slowest 20% of the subjects.<sup>2</sup>

Older subjects with three or more of these characteristics were classified as frail and those with one or two characteristics as pre-frail.<sup>2</sup>

The study by Fried et al.<sup>2</sup> proposed cutoff points for the criteria of weakness, low physical activity and slowness criteria, since

calculation of these criteria depends on the anthropometric variables and intrinsic characteristics of each population. However, in this study we chose to calculate specific cutoff points for the sample and compared them with the values obtained by Fried et al.<sup>2</sup>

### Ethics

Our study was approved by the Ethics Committee of the University Hospital, Ribeirão Preto Medical School, University of São Paulo. Written informed consent was obtained from all participants.

### Statistics

Descriptive data were analyzed: means and standard deviations (SD) were used for continuous variables and proportions were calculated for categorical variables. Differences between frail groups were investigated using the Fisher exact test for categorical variables, and analysis of variance (ANOVA) followed by the Bonferroni test was used for continuous and parametric variables. All analyses were carried out using the SAS 9.0 software, and the significance level was set at  $P < 0.05$ .

### RESULTS

A total of 385 individuals were studied, among whom 249 (64.7%) were women. The overall mean age of the participants was  $73.9 \pm 6.5$  years, with means of  $74.0 \pm 6.6$  years for men and  $73.9 \pm 6.5$  years for women ( $P = 0.84$ ). The participants were predominantly white (68.2%), had 1 to 4 years of schooling (54.3%), were married (58.4%) and had four or more children (46.2%) (Table 1).

In this study population, systemic arterial hypertension was the most common self-reported disease (46.2%), followed by urinary incontinence (30.9%) and osteoporosis (21.3%). More than one third of the participants reported that they took four or more medications per day (Table 1).

According to the frailty criteria used in the present study, 9.1% of the sample was considered frail, 49.6% pre-frail and 41.3% non-frail. The mean age was  $72.2 \pm 5.9$ ,  $74.7 \pm 6.4$  and  $77.7 \pm 7.6$  years for the non-frail, pre-frail and frail groups, respectively ( $P < 0.01$ ). Post-test analysis showed that there were differences in age between all groups: frail versus non-frail ( $P < 0.01$ ), frail versus pre-frail ( $P = 0.01$ ) and non-frail versus pre-frail ( $P = 0.01$ ).

Regarding the frailty criteria, 12.5% were positive for weight loss over the last year, 20.5% for exhaustion, 17.1% for slowness, 24.4% for low physical activity and 20.5% for weakness. The exhaustion criterion was mainly reported by females ( $P < 0.001$ ), whereas no difference between the sexes was observed for the remaining criteria.

The cutoff points for weakness and slowness calculated for our elderly population are shown in Tables 2 and 3. For the criterion of low physical activity, women with a Minnesota value of

**Table 1.** Characteristics of the study population (n = 385)

Variable	Men		Women		All	
	n = 136	%	n = 249	%	n = 385	%
<b>Ethnicity</b>						
Caucasians	96	70.6	167	67.1	263	68.2
Others	40	29.4	82	32.9	122	31.7
<b>Schooling (years)</b>						
0	22	16.2	57	22.9	79	20.5
1 to 4	74	54.4	135	54.2	209	54.3
5 to 12	29	21.3	40	16.0	69	17.9
13 or over	11	8.1	17	6.8	28	7.3
<b>Marital status</b>						
Single	7	5.1	19	7.6	26	6.7
Married	110	80.9	115	46.2	225	58.4
Widowed	14	10.3	97	39.0	111	28.8
Divorced	5	3.7	18	7.2	23	6.1
<b>Number of children</b>						
0	12	8.8	27	10.8	39	10.1
1	13	9.6	18	7.2	31	8.0
2 or 3	53	39.0	84	33.8	137	35.6
4 or more	58	42.6	120	48.2	178	46.2
<b>Reported diseases</b>						
Heart disease	17	12.5	31	12.4	48	12.5
Hypertension	60	44.1	118	47.4	178	46.2
Stroke	4	2.9	4	1.6	8	2.1
Diabetes	23	16.9	44	17.7	67	17.4
Cancer	6	4.4	5	2	11	2.9
Arthritis	15	11.0	48	19.3	63	16.4
Depression	13	9.6	60	24.1	73	18.9
Respiratory disease	13	9.6	13	5.2	26	6.7
Osteoporosis	6	4.4	76	30.5	82	21.3
Urinary incontinence	33	24.3	86	34.5	119	30.9
<b>Number of medications</b>						
0	23	16.9	22	8.8	45	11.7
1	32	23.5	34	13.7	66	17.1
2	22	16.2	41	16.5	63	16.4
3	14	10.3	43	17.3	57	14.8
4 or more	45	33.1	108	43.4	154	39.7

**Table 2.** Reference values for hand grip strength score

BMI (kg/m <sup>2</sup> )	Cutoff (kgf)	
	Men	Women
≤ 23	< 17.33	< 12.87
> 23 to ≤ 28	< 24.93	< 14.27
> 28 to ≤ 30	< 28.27	< 10.53
> 30	< 18	< 16.40

BMI = body mass index; kgf = kilogram force.

**Table 3.** Reference values for slowness score (4.6-m walk test)

Height (cm)	Cutoff (seconds)
Men < 168	> 4.88
Men > 168	> 4.97
Women < 155	> 5.73
Women > 155	> 6.33

0 (zero) kcal/week and men with values below 107.49 kcal/week were scored as frail.

Analysis on the associations between the sociodemographic variables listed in **Table 1** and frailty did not reveal any differences between the levels of the syndrome ( $P > 0.05$ ). There were associations between frailty and stroke ( $P = 0.02$ ), diabetes ( $< 0.001$ ), neoplasia ( $P = 0.02$ ), osteoporosis ( $P = 0.007$ ), urinary incontinence ( $P = 0.001$ ) and fecal incontinence ( $P = 0.002$ ). The elderly subjects who were considered to be frail attended more medical visits ( $P = 0.03$ ) and had a greater chance of having been hospitalized ( $P < 0.001$ ) within the 12 months preceding the interview than did non-frail and pre-frail subjects. No difference was observed between the frail, pre-frail and non-frail groups regarding the number of medications used ( $P = 0.54$ ) (**Table 4**).

## DISCUSSION

In this study, 9.1% of the sample was frail, 49.6% pre-frail and 41.3% non-frail. Data regarding frailty syndrome are necessary for planning public health policies, since this is considered to be a clinical, non-unidirectional and potentially reversible syndrome.<sup>17</sup> Early recognition and adoption of proactive measures at different stages of the process can prevent or delay the occurrence of adverse health outcomes. In Brazil, this information was scarce before the creation of the FIBRA Network project, to which the present study belongs.

The prevalence of the frailty syndrome differed according to the region studied. In Santa Cruz, a city in the state of Rio Grande do Norte, the prevalence of frailty was found to be 17.1%. This value is higher than those found in developed countries, perhaps as a result of exposure to various adverse factors and stressors that typically affect people's lives in that region.<sup>4</sup> The SABE 2000 study, conducted in the city of São Paulo, evaluated 688 elderly individuals aged 75 years or over and found that the prevalence of frailty was 29.5% and pre-frailty, 50.6%.<sup>18</sup> The large number of frail subjects in that study was due, in part, to the greater age of the sample. Moreover, the prevalence of frailty was 9% in Campinas, state of São Paulo, a city with 1.1 million inhabitants,<sup>13</sup> and 8.7% in Belo Horizonte, state of Minas Gerais state,<sup>14</sup> which has around 2.3 million. These rates were similar to those detected in the present study. All of these cities have high human development indexes (HDI).<sup>13,14,18</sup>

The prevalence of the components of frailty syndrome tends to be higher in places with a low HDI.<sup>13</sup> The percentage of frailty syndrome detected in the population of the present study was similar to that observed in developed countries.<sup>2,3</sup> This may partly be explained by the high HDI of the city of Ribeirão Preto, which is considered to be one of the highest in the state of São

**Table 4.** Associations between self-reported health conditions and frailty syndrome

Variable	Non-frail		Pre-frail		Frail		P
	n = 159	%	n = 191	%	n = 35	%	
Heart diseases	15	9.4	24	12.6	9	25.7	0.09
Hypertension	70	44.0	91	47.6	17	48.6	0.81
Stroke	0	0	5	2.6	3	8.6	0.02
Diabetes	15	9.4	38	19.9	14	40.0	< 0.001
Cancer	3	1.9	4	2.1	4	11.4	0.02
Arthritis	22	13.8	32	16.7	9	2.6	0.51
Depression	8	5.0	12	6.3	6	1.7	0.10
Respiratory diseases	27	17.0	34	17.8	12	3.4	0.14
Osteoporosis	26	16.4	41	21.5	15	42.9	0.007
Urinary incontinence	33	20.8	71	37.2	15	42.9	0.001
Fecal incontinence	2	1.3	4	2.1	4	11.4	0.002
Number of medications per day							
0	25	15.7	18	9.4	2	5.7	0.54
1	36	22.7	25	13.1	5	14.3	
2	26	16.3	31	16.2	6	17.2	
3	23	14.5	30	15.7	4	11.4	
4+	49	30.8	87	45.6	18	51.4	
Number of doctor visits over the last 12 months							
0	18	11.3	15	7.9	0	0	0.03
1 to 4	101	63.5	115	60.2	18	51.4	
5 or more	40	25.2	61	31.9	17	48.6	
Hospitalization over the last 12 months							
Yes	22	13.8	37	19.4	15	42.8	< 0.001
No	137	86.2	154	80.6	20	57.2	

Paulo and in Brazil, and close to what is seen in developed countries.<sup>2,3</sup> In contrast, in places where the HDI is considered to be medium or low, there is a high prevalence of frailty. Sousa et al. believed that prevalences of frailty higher than those found in developed countries may be due to lifelong exposure to different adverse and stressful factors that are characteristic of vulnerable regions.<sup>4</sup> Factors such as precarious social conditions, childhood lived in poverty, adverse working conditions during adulthood, situations of health risk and violence may indirectly interfere with the development of subclinical inflammatory processes and with the immune response to stress. These processes are closely linked to frailty<sup>4</sup>.

Frailty was significantly associated with age. Many studies have shown the influence of aging on the process of becoming frail.<sup>2,19-21</sup> Advancing age is a complex phenomenon that it is difficult to classify into different levels. It is associated with progressive loss of homeostatic and hemodynamic regulation, which makes the body less resilient, and often not at all resilient, to adverse situations, depending on the functional reserves of different physiological systems. It is in this context that the frailty syndrome arises.<sup>22</sup> Thus, implementation of diagnostic efforts and early intervention regarding the consequences of normal and

pathological decline due to aging is unquestionably an important public health issue.

No other association between frailty and sociodemographic variables was detected in the present study, probably because there was some homogeneity of schooling and family characteristics among the older subjects of this population. Woo et al. observed that the frailty index was higher among subjects of low educational level, with low income and with inadequate financial situations.<sup>23</sup> Espinoza et al. observed an association between low schooling levels and the onset of new cases of frailty, while Bilotta et al. reported that the syndrome was associated with age, female sex, widowhood, dependence on other people for activities of daily living, depression, comorbidities and use of several medications.<sup>6,9</sup>

In the present study, only 7% of the subjects who were considered to be frail did not have any chronic disease, and 25% of this group reported having hypertension. The frail group attended more medical visits than the non-frail group. Associations with stroke, diabetes, neoplasia and urinary and fecal incontinence were also observed. Individuals presenting frailty syndrome have lower capacity to respond to adverse events, possibly due to reduced functional reserves. Frail elderly

people are recognized to be at high risk of adverse health results and to have impaired ability to tolerate hospitalization and invasive procedures. Thus, this group has accentuated needs for health services, care and institutionalization, as well as high mortality.<sup>24</sup> Furthermore, with aging, the number of visits to doctors increases considerably. People aged 75 years or over attend around seven visits to doctors per year for monitoring of both acute and chronic illnesses.<sup>25</sup>

The relationship between frailty and chronic diseases is complex. The terms primary and secondary frailty have been used to characterize frailty in the absence or presence of chronic diseases. The number of older people with primary frailty is very small. More importantly, development of diseases can precipitate frailty through requiring mobilization of resources by the organism, with consequences for the functional reserves. The development of characteristics of frailty is evident in the advanced stages of many diseases.<sup>26</sup>

In the present study, the most prevalent criterion of frailty syndrome was low physical activity, followed by weakness and exhaustion. The prevalence of the criteria varies according to the population studied, although weakness characterized by low handgrip strength has been the most prevalent criterion in many studies, underscoring the importance of muscle strength in the genesis of the syndrome.<sup>27-29</sup>

In an investigation on the early manifestations and development of frailty phenotype in women, Xue et al. reported that the incidence of frailty among women who were non-frail at the beginning of the study was 9%.<sup>29</sup> Despite the heterogeneity observed, weakness was the most common initial manifestation and its occurrence together with slowness and low physical activity preceded exhaustion and weight loss in 76% of the women who were not frail at the beginning of the study.<sup>29</sup> These findings suggest that weakness can serve as a sign of increased vulnerability in the initial stages of frailty.

The specific cutoff points for the criteria of weakness, slowness and low physical activity that were calculated in this study were lower than those proposed by Fried et al.<sup>2</sup> These lower values may perhaps be due to the lower values of the anthropometric variables of height and BMI that were used for calculating these parameters.

In a study on frailty, Santos calculated specific cutoff values for his sample regarding the criteria of gait time and handgrip strength.<sup>20</sup> When these specific cutoff points were used, the frequencies of frail, pre-frail and non-frail subjects were very similar to those observed in the study by Fried et al.<sup>2</sup> However, there were higher frequencies of frail and pre-frail subjects and a lower frequency of non-frail subjects when the reference values proposed by Fried et al. were used.<sup>2</sup> This indicates that these cutoff points should be adjusted for the

population studied because of the specificity of the anthropometric measurements involved.

The Minnesota Leisure Time Activities Questionnaire, which has already been validated in Brazil,<sup>16</sup> is a long questionnaire that covers some activities little practiced by elderly Brazilians. This characteristic may have influenced the very low cutoff points detected for this criterion. However, it is important to recognize that the elderly population studied here presented low physical activity levels and that changing this condition is an important goal to be achieved.

Women had worse performance regarding the criteria involving physical effort, i.e. they were slower and had lower energy consumption and lower grip strength in this study. However, because of the lower cutoff points for women than for men regarding these criteria, this difference did not affect the women's syndrome scores. The only criterion that was significantly more present among women was fatigue.

It is of fundamental importance to recognize frailty syndrome in elderly populations in view of these individuals' high susceptibility to stressful events. There may be the possibility of halting or even reversing the progression of the syndrome. Although the results from the present study cannot be applied to populations with different characteristics, they may be useful for making estimates for use in medium-sized urban populations and may be of help in drawing up public policies.

The main limitation of this study was its cross-sectional nature, which did not allow any temporal relationship between the variables to be established. On the other hand, cross-sectional studies are important in order to show the burden of frailty in the population and the factors associated with such cases, as done in the present investigation. Studies with this design are subject to survival bias, which could lead to underestimation of the associations observed.

Another limitation that can be mentioned was our decision to exclude patients who were already known to be dependent. This may have influenced the frailty rate obtained. However, this was a decision based on our interest in evaluating frail and potentially vulnerable individuals among independent elderly subjects, since these individuals are not identified through conventional evaluation.

## CONCLUSION

The percentage of frailty syndrome detected in the population of the present study, which was independent for basic activities of daily living, was similar to that observed in developed countries. Frailty was associated with more advanced age, previous stroke and presence of diabetes, neoplasia and urinary and fecal incontinence. Frail elderly individuals attended more visits to doctors and had a higher chance of hospitalization over the

past year than did the pre-frail and non-frail groups. The cutoff points detected for weakness, slowness and low physical activity were lower than those proposed by Fried et al., thus indicating that these cutoff points should be adjusted for the population studied. The present study provides data to support public health strategies for early detection of pre-frailty and frailty in Brazilian cities, with a focus on appropriate interventions for prevention and reversal of this syndrome, thereby reducing complications, hospitalizations and mortality.

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# Cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people: a cross-sectional study

Fatores de risco cardiovasculares associados à síndrome de fragilidade em idosos hospitalizados: um estudo transversal

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## KEY WORDS:

Frail elderly.  
Risk factors.  
Cardiovascular diseases.  
Aging.  
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## PALAVRAS-CHAVE:

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Doenças cardiovasculares.  
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## ABSTRACT

**CONTEXT AND OBJECTIVE:** Identification of frailty syndrome and its relationship with cardiovascular risk factors among hospitalized elderly people is important, since this may contribute towards broadening of knowledge regarding this association within tertiary-level services. This study aimed to evaluate the cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people.

**DESIGN AND SETTING:** Observational cross-sectional study in a public teaching hospital.

**METHODS:** The participants were elderly patients admitted to clinical and surgical wards. The cardiovascular risk factors assessed were: body mass index (BMI), waist circumference, systemic arterial hypertension (SAH), blood glucose, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and triglycerides. To identify frailty syndrome, the method proposed by Fried was used. The data were analyzed through descriptive statistics, chi-square test ( $P < 0.10$ ) and multinomial logistic regression ( $P < 0.05$ ).

**RESULTS:** A total of 205 individuals were evaluated. It was found that 26.3% ( $n = 54$ ) of the elderly people were frail, 51.7% ( $n = 106$ ) were pre-frail and 22% ( $n = 45$ ) were non-frail. The preliminary bivariate analysis ( $P < 0.10$ ) for the regression model showed that frailty was associated with BMI ( $P = 0.016$ ), LDL cholesterol ( $P = 0.028$ ) and triglycerides ( $P = 0.093$ ). However, in the final multivariate model, only overweight remained associated with the pre-frail condition (odds ratio, OR = 0.44; 95% confidence interval, CI = 0.20-0.98;  $P = 0.045$ ).

**CONCLUSION:** States of frailty were highly present in the hospital environment. The pre-frail condition was inversely associated with overweight.

## RESUMO

**CONTEXTO E OBJETIVO:** A identificação da síndrome de fragilidade em idosos hospitalizados em interface com fatores de risco cardiovascular é relevante, pois pode contribuir para a ampliação do conhecimento sobre essa relação no nível de serviço terciário. Este estudo objetivou avaliar os fatores de risco cardiovascular associados à síndrome de fragilidade em idosos hospitalizados.

**TIPO DE ESTUDO E LOCAL:** Estudo observacional transversal em hospital público de ensino.

**MÉTODOS:** Participaram idosos internados nas clínicas médica e cirúrgica. Os fatores de risco cardiovascular avaliados foram: índice de massa corporal (IMC), circunferência abdominal, hipertensão arterial sistêmica (HAS), glicemia, colesterol total, lipoproteínas de alta densidade (HDL), lipoproteínas de baixa densidade (LDL) e triglicérides. Para identificar a síndrome de fragilidade, utilizou-se o método proposto por Fried. Os dados foram analisados por estatística descritiva, teste qui-quadrado ( $P < 0,10$ ) e regressão logística multinomial ( $P < 0,05$ ).

**RESULTADOS:** Foram incluídos 205 indivíduos. Constatou-se que 26,3% ( $n = 54$ ) dos idosos eram frágeis, 51,7% ( $n = 106$ ) pré-frágeis e 22% ( $n = 45$ ) não frágeis. A análise bivariada preliminar ( $P < 0,10$ ) para o modelo de regressão indicou associações da fragilidade com as variáveis IMC ( $P = 0,016$ ), colesterol LDL ( $P = 0,028$ ) e triglicérides ( $P = 0,093$ ). Entretanto, no modelo multivariado final, apenas a variável excesso de peso permaneceu associada à condição de pré-fragilidade (*odds ratio*, OR = 0,44; intervalo de confiança, IC 95% = 0,20-0,98;  $P = 0,045$ ).

**CONCLUSÃO:** Os estados de fragilidade apresentaram-se elevados em ambiente hospitalar. A condição de pré-fragilidade foi inversamente associada ao excesso de peso.

## INTRODUCTION

Frailty among elderly people can be understood as a clinical syndrome. It is characterized as a state of increased vulnerability to stressors that results from decreased physiological reserves and imbalances in multiple systems.<sup>1-2</sup>

Seeking to increase knowledge regarding this condition has become a worldwide investigative aim for researchers,<sup>3</sup> since frailty may cause higher risk of health problems, hospitalization and mortality, as well as family overload and increased use of healthcare systems.<sup>4</sup>

A review indicated that cardiovascular diseases is a factor associated with frailty syndrome, since the prevalence of cardiovascular conditions may range from 25% to 50% among frail elderly people.<sup>5</sup> Furthermore, the association between these conditions is bidirectional<sup>6</sup> and low level chronic inflammation is present in both conditions.<sup>5</sup>

In a study involving community-living elderly people in England, it was found that the lowest frailty rate was among those with body mass index (BMI) 25-29.9 kg/m<sup>2</sup>. Elderly people with high waist circumference measurement were significantly more frail.<sup>3</sup> Another population-based study in Great Britain reported higher odds of obesity, high waist circumference, low high-density lipoprotein-cholesterol (HDL) and hypertension among frail elderly men than among non-frail men.<sup>7</sup>

In Brazil, a study conducted in 17 cities found that BMI and abdominal circumference were associated with frailty, although obesity did not present any significant association.<sup>8</sup> Additionally, in a study among community-living elderly people, frailty was associated with higher blood pressure, larger abdominal circumference and low blood HDL levels. Cardiovascular risk factors such as BMI, low-density lipoprotein (LDL) levels, total cholesterol and triglycerides were not associated with frailty.<sup>9</sup> In a study carried out among hospitalized elderly people, BMI and arterial systemic hypertension were not associated with frailty syndrome.<sup>10</sup>

Thus, the findings from studies conducted in Brazil and in other countries are contradictory, which highlights the need for more studies in this area. Furthermore, most of the investigations have assessed community-living elderly people.<sup>2,3,7-9</sup> There is a gap in the literature with regard to the hospital context, especially for the Brazilian elderly population.

Early identification of frailty syndrome among elderly people and correlation of its occurrence with cardiovascular risk factors may prevent disease progression and adverse outcomes.<sup>11</sup> Within the hospital context, this knowledge can help in planning interventions for frail elderly people, with the aim of reducing the duration of hospitalization and occurrences of rehospitalization.

## OBJECTIVE

The aim of this study was to ascertain the cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people.

## METHODS

This was an observational analytical cross-sectional study that formed part of a larger project entitled "Study of Frailty in Elderly People (EFRAGI)", funded by the National Council for Scientific and Technological Development (CNPq). The protocol was approved by the ethics committee of Universidade Federal do Triângulo Mineiro (UFTM) (document no. 2511). The interviewers approached the elderly individuals in the hospital, presented the study aims and explained the consent form, so as to make sure that there were no doubts regarding the research protocol, and then asked the patient to sign the consent form. Individuals were included when they were 60 years of age or over and were hospitalized in the clinical and surgical wards of a public teaching hospital in the city of Uberaba, located in the state of Minas Gerais, Brazil.

The sample size was calculated in accordance with the main objectives of the EFRAGI study. The prevalence of frailty was taken to be 30%, as observed in previous studies in hospital environments,<sup>12,13</sup> with a precision of 5% and a confidence interval of 95% in a finite population of 1,455 elective elderly patients. The sample size required was found to be 265 elderly individuals. Moreover, a sample loss of 50% was taken into consideration and therefore the maximum number of interviews was 530. The recruitment process was carried out by means of systematic random sampling, with a sampling interval of 2. The elderly individuals were included in a chronologically organized list that took the time of hospitalization into consideration: the first individual was randomly chosen and the next was excluded; the third was included and the fourth was excluded; and the same pattern was followed until the end of the list.

The data collection encompassed the period from April 2013 to March 2014. The inclusion criteria were that the patients needed to be 60 years or over, without cognitive impairment, and needed to have agreed to participate in the study. Elderly individuals who presented restrictions on walking due to their recovery from surgery were interviewed on the next day. The exclusion criteria comprised the presence of severe cognitive impairment or Pfeffer scores greater than or equal to six, in association with absence of a caregiver; stroke sequelae with localized impairment of strength and aphasia; severe or unstable Parkinson disease associated with severe impairment of mobility, speech or illness that made it impossible to conduct the tests; end-of-life status, with severe impairment of vision and hearing; new hospitalization of an elderly individual who had already been included in the study; and presence of limitations regarding walking and talking.

Over the data collection period of the study, 445 patients were found to be eligible, but only 205 participated in the study because of losses and exclusions: refusal to participate (75), cognitive impairment without a caregiver (57), Pfeiffer greater than or equal to more than six (44), absence of blood samples (50) and other reasons (14). Blood samples were collected on the day after data collection, by hospital laboratory staff. The patients who were excluded because no blood samples had been taken were discharged before the blood sample could be taken.

Before the beginning of the interview, cognitive impairment was assessed using the Mini-Mental State Examination (MMSE),<sup>14</sup> which has been translated and validated for use in Brazil. This instrument is scored on a scale from zero to thirty points, and takes into consideration the elderly individual's schooling level: 13 points for illiterate individuals, 18 points for individuals with one to 11 years of schooling and 26 points for individuals with more than 11 years of schooling.<sup>14</sup> In addition, if the elderly individuals presented cognitive impairment, as assessed through the MMSE, the Pfeiffer questionnaire<sup>15</sup> was filled out by the individual's caregiver. The Pfeiffer questionnaire consists of an 11-question scale that is designed to evaluate elderly individuals' ability to perform some activities. The maximum score of this scale is 33 points, and it verifies the presence and severity of the cognitive impairment, considering functionality and the need for assistance from other people. In this study, the interview was conducted when the Pfeiffer results were below six points, and supplementary information was requested from the caregiver, whenever necessary.

A structured questionnaire was used to obtain sociodemographic, economic and health data. The individuals who were able to walk underwent anthropometric evaluation consisting of measurements of weight, height and BMI. The patients who were unable to walk were assessed through estimated heights and weights using the equations proposed by Rabito et al.<sup>16</sup> for assessing hospitalized individuals. The weight estimate calculation included arm circumference, abdominal circumference, calf circumference and arm semi-span.<sup>16</sup>

Nutritional status was classified using the BMI, and the cutoff points used were: underweight (BMI  $\leq$  22 kg/m<sup>2</sup>), normal weight (BMI between 22 and 27 kg/m<sup>2</sup>) and overweight (BMI  $>$  27 kg/m<sup>2</sup>).<sup>17</sup> In order to classify the patients based on abdominal circumference, the cutoff values of 102 cm and 88 cm, for men and women respectively, were used to consider whether an individual presented abdominal obesity.<sup>18</sup>

A blood sample was obtained within the first 24 hours of hospitalization, for a biochemical assessment. The patients' lipid profiles were interpreted in accordance with the Fifth Guidelines on Prevention of Dyslipidemia and Atherosclerosis,

issued by the Brazilian Society of Cardiology.<sup>19</sup> In order to consider that values were outside of their normal range, the following criteria were used: total cholesterol  $>$  200 mg/dl; LDL (low-density lipoprotein cholesterol)  $>$  100 mg/dl; HDL (high-density lipoprotein cholesterol)  $<$  40 mg/dl; and triglycerides  $>$  150 mg/dl. Fasting glycemia<sup>20</sup> was considered altered when the value was above 100 mg/dl.

The presence of frailty syndrome was ascertained using a five-component phenotype proposed by Fried et al.,<sup>1</sup> as follows:

1. **Unintentional weight loss**, assessed by means of the question "In the last year, did you unintentionally lose 4.5 kg or more (i.e. without diets or exercise)?"
2. **Decreased muscle strength**, verified through handgrip strength, which was assessed through three measurements presented in kilograms-force (kgf), with one-minute intervals between the measurements. The average value from the three measurements was taken and the cutoff point proposed by Fried et al.<sup>1</sup> was used.
3. **Self-reported exhaustion**, assessed through two questions from the Brazilian version of the depression scale of the Center for Epidemiological Studies (CES-D):<sup>21</sup> "Have you felt that you had to make an effort to complete your daily activities?" and "Were you unable to carry on with your things?" The participants were asked how they felt in the past week regarding these two questions, and the responses were obtained on a scale from 0 to 3, in which never or rarely was equal to 0; sometimes = 1; frequently = 2; and always = 3. Questions scored as two or three fulfilled this frailty criterion.
4. **Walking slowness**, which was assessed through the time taken to walk a 4.6 m distance, in seconds. The elderly individuals walked 8.6 m, and neither the initial nor the final two meters was taken into consideration in calculating the time taken. Furthermore, three measurements were made and the average value between them was used in the classification. This classification took into consideration the cutoff points proposed by Fried et al.<sup>1</sup>
5. **Low physical activity level**, which was ascertained through the long version of the International Physical Activity Questionnaire (IPAQ), as adapted for use in elderly populations.<sup>22</sup> The classification adopted for this component followed the recommendations of the American College of Sports Medicine and the American Heart Association. These associations consider individuals to be "active" if they participate in more than 150 minutes of physical activities in a week, and "inactive" if they participate in zero to 149 minutes of physical activities in a week.<sup>23</sup>

The elderly individuals were considered to be frail when they presented three or more of the abovementioned

components; pre-frail when they presented one or two components; and non-frail when they did not present any of the five components.<sup>1</sup>

The variables studied were:

1. social, demographic and economic: gender (male and female), age (60-70; 70-80; or 80 years and over), marital status (single, married/living with a partner, widower or divorced), number of years of schooling (none; 1-4; 4-8; 8; 9-11; or 11 or more) and monthly income in minimal wages (no income; < 1; 1-3; 3-5; or > 5);
2. self-reported morbidity: systemic arterial hypertension;
3. nutritional status, as assessed using the BMI: underweight, normal weight or overweight;
4. abdominal circumference in cm;
5. glycemic level in mg/dl;
6. total cholesterol in mg/dl;
7. HDL in mg/dl;
8. LDL in mg/dl;
9. triglycerides in mg/dl; and
10. frailty classification (non-frail, pre-frail and frail).

The data were input with double entry, to check for any inconsistencies. The stored data were then imported to the Statistical Package for the Social Sciences (SPSS) software, version 17.0, for analysis.

The nominal variables were analyzed using absolute and percentage frequencies. Moreover, in order to identify the risk factors associated with the condition of pre-frailty or frailty, a preliminary bivariate analysis was carried out using the chi-square test, in which the results were considered significant when  $P < 0.10$ . Thus, the variables identified ( $P < 0.10$ ) were included in a multivariate regression model. In addition, the factors that were associated with the pre-frail or frail conditions were identified by means of multivariate analysis using the prevalence odds ratio, which was ascertained through multinomial logistic regression (saturated model), taking a significance level of 5% and confidence interval of 95%. The predictors were: SAH, BMI, abdominal circumference, glycaemia, total cholesterol, HDL, LDL and triglycerides.

## RESULTS

The prevalence of the non-frail condition among elderly individuals was 22% ( $n = 45$ ). The prevalence of the pre-frail condition was 51.7% ( $n = 106$ ) and the prevalence was 26.3% ( $n = 54$ ) for non-frail individuals. Furthermore, there was a higher prevalence of frail female elderly individuals, while among non-frail and pre-frail individuals, there was higher prevalence of men. The marital status of widower accounted for 33.3% of the frail elderly people (Table 1). Our sample was mainly composed of individuals in the age category 60-70 years who were married or

living with a partner, with schooling level of 1-4 years and with individual monthly income of one minimum wage (Table 1). The distribution of the social and demographic data for each frailty level is displayed in Table 1.

Regarding the associated factors, the variables that were accepted in the preliminary bivariate analysis, in accordance with the inclusion criterion ( $P < 0.10$ ), were: BMI ( $P = 0.016$ ), LDL ( $P = 0.028$ ) and triglycerides ( $P = 0.093$ ) (Table 2). Therefore, these factors were included in the multivariate analysis.

The variables relating to cardiovascular risk factors and their associations with frailty level are presented in Table 2.

In the multivariate model, overweight was inversely associated with the pre-frail condition ( $P = 0.045$ ). Nevertheless, no other variables presented associations with frailty syndrome (Table 3). The variables included in the multivariate logistic regression ( $P < 0.05$ ) are displayed in Table 3.

**Table 1.** Distribution of social, demographic and economic variables in each frailty level among hospitalized elderly individuals. Uberaba, MG, Brazil, 2013

Variables	Non-frail		Pre-frail		Frail		Total		P*
	n	%	n	%	n	%	n	%	
<b>Gender</b>									
Male	30	66.7	68	64.2	26	48.1	124	60.5	0.093
Female	15	33.3	38	35.8	28	51.9	81	39.5	
<b>Age</b>									
60-70	34	75.6	66	62.3	29	53.7	129	62.9	0.057
70-80	10	22.2	36	34.0	18	33.3	64	31.2	
80 or over	1	2.2	4	3.8	7	13.0	12	5.9	
<b>Marital status</b>									
Single	2	4.4	5	4.7	2	3.7	9	4.4	0.138
Married/ living with partner	27	60.0	72	67.9	25	46.3	124	60.5	
Widowed	11	24.4	14	13.2	18	33.3	43	21.0	
Divorced	5	11.1	15	14.2	9	16.7	29	14.1	
<b>School years</b>									
No schooling	4	8.9	24	22.6	13	24.1	41	20.0	0.101
1-4	27	60.0	59	55.7	32	59.3	118	57.6	
4-8	5	11.1	11	10.4	1	1.9	17	8.3	
8 years	3	6.7	5	4.7	1	1.9	9	4.4	
9-11	1	2.2	1	0.9	3	5.6	5	2.4	
11 or more	5	11.1	6	5.7	4	7.4	15	7.4	
<b>Individual monthly income</b>									
No income	1	2.2	6	5.7	2	3.7	9	4.4	0.167
< 1	-	-	5	4.7	1	1.9	6	2.9	
1	22	48.1	60	56.6	33	61.1	115	56.1	
1-3	19	42.2	28	26.4	18	33.3	65	31.7	
3-5	2	4.4	5	4.7	-	-	7	3.4	
> 5	1	2.2	2	1.9	-	-	3	1.5	

\*Chi-square test.

**Table 2.** Cardiovascular risk factors associated with frailty level in hospitalized elderly individuals. Uberaba, MG, Brazil, 2013

Variables	Non-frail		Pre-frail		Frail		p*
	n	%	n	%	n	%	
<b>SAH</b>							
Yes	28	62.2	66	62.3	41	75.9	0.191
No	17	37.8	40	37.7	13	24.1	
<b>BMI</b>							
Underweight ( $\leq 22$ kg/m <sup>2</sup> )	3	6.7	27	25.5	13	24.1	0.016
Normal weight (22-27 kg/m <sup>2</sup> )	14	31.1	41	38.7	15	27.8	
Overweight ( $> 27$ kg/m <sup>2</sup> )	28	62.2	38	35.8	26	48.1	
<b>Abdominal circumference<sup>†</sup></b>							
Normal	23	51.1	55	51.9	22	40.7	0.386
Abdominal obesity	22	48.9	51	48.1	32	59.3	
<b>Glycemia</b>							
$\leq 100$ mg/dl	24	53.3	45	42.5	17	32.1	0.104
$> 100$ mg/dl	21	46.7	61	57.5	36	67.9	
<b>Total cholesterol</b>							
$\leq 200$ mg/dl	32	71.1	78	73.6	47	87.0	0.102
$> 200$ mg/dl	13	28.9	8	6.4	47	87.0	
<b>HDL</b>							
$> 40$ mg/dl	21	46.7	52	49.1	21	38.9	0.471
$\leq 40$ mg/dl	24	53.3	54	50.9	33	61.1	
<b>LDL</b>							
$\leq 100$ mg/dl	25	55.6	51	48.1	38	70.4	0.028
$> 100$ mg/dl	20	44.4	55	51.9	16	29.6	
<b>Triglycerides</b>							
$\leq 150$ mg/dl	27	60.0	77	72.6	43	79.6	0.093
$> 150$ mg/dl	18	40.0	29	27.4	11	20.4	

\*P < 0.10; <sup>†</sup>Cutoff values of 102 cm and 88 cm, for men and women respectively, were used to consider that individuals presented abdominal obesity;<sup>18</sup> SAH = systemic arterial hypertension, BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

**Table 3.** Final logistic multinomial regression model on the association between cardiovascular risk factors and pre-frail and frail conditions among hospitalized elderly individuals in Uberaba, MG, Brazil, 2013

Variables	Pre-frail			Frail		
	OR	95% CI	P*	OR	95% CI	P*
<b>BMI</b>						
Underweight ( $\leq 22$ kg/m <sup>2</sup> )	2.93	0.76-11.35	0.118	3.55	0.82-15.35	0.089
Normal weight (22-27 kg/m <sup>2</sup> )		1			1	
Overweight ( $> 27$ kg/m <sup>2</sup> )	0.44	0.20-0.98	0.045*	0.96	0.38-2.42	0.937
<b>LDL</b>						
$\leq 100$ mg/dl		1			1	
$> 100$ mg/dl	1.83	0.85-3.91	0.118	0.67	0.28-1.61	0.375
<b>Triglycerides</b>						
$\leq 150$ mg/dl		1			1	
$> 150$ mg/dl	0.61	0.28-1.35	0.223	0.49	0.19-1.25	0.136

OR = odds ratio; CI = confidence interval; 1: reference category; Non-frail: reference category; \*P < 0.05; BMI = body mass index; LDL = low-density lipoprotein.

## DISCUSSION

The prevalence of frail and pre-frail conditions among hospitalized elderly people differs between studies conducted in Brazil and elsewhere in the world.<sup>10,24,25</sup> A study conducted in a Brazilian city found that the highest percentage (49.5%) of the elderly subjects were considered pre-frail,<sup>10</sup> which corroborates the findings of the present study. Moreover, other investigations on hospitalized elderly people in Belgium<sup>24</sup> and Norway<sup>25</sup> obtained similar results, with values between 58.5% and 47.7%. However, the percentages of frail elderly individuals were higher in those investigations<sup>10,24</sup> than in the present study (46.5%; 40%). These conflicting prevalences may be explained by differences in the inclusion criteria and in the diagnostic criteria for identifying frailty syndrome. Moreover, the age groups were also different, which were over 65 years<sup>10</sup> and over 70 years.<sup>24</sup> Additionally, the regional specificities of health status impairment among hospitalized elderly people may explain the differences between the findings.

The rate of occurrence of frailty syndrome may vary according to social, demographic and economic characteristics, as demonstrated in the descriptive data analysis. The predominance of frail women agrees with the findings from another Brazilian study<sup>4</sup> conducted in a hospital, which showed that 63.6% of the frail elderly subjects were women. That study used the Edmonton Frail Scale (EFS) to make assessments. Moreover, in a recent literature review,<sup>26</sup> female gender was positively associated with frailty. Therefore, this finding corroborates the hypothesis that women present more intense muscle mass loss due to ageing, since the changes in the estrogen levels after the menopause contribute towards this condition.<sup>27,28</sup>

Regarding marital status, the highest percentage of the frail elderly individuals consisted of widowers. This finding is supported by a Brazilian study<sup>4</sup> conducted in hospital settings, in which 53.1% of the elderly subjects presenting severe frailty were single, divorced or widowers.

Among community-living elderly people, a similar result was found in an investigation in Taiwan, which found that 53% of the frail elderly individuals were widowers.<sup>29</sup> Moreover, frailty syndrome involves complex interactions that include not only clinical factors but also social factors.<sup>30</sup> Therefore, social support components such as widower status should be considered to be potential causal factors for the development of frailty syndrome.

The association between frailty syndrome and BMI, among individuals with low and high BMI, has been discussed in the literature.<sup>3</sup> One investigation found that there was a strong positive association between BMI and frailty status at the baseline, in which participants who were overweight and obese were identified as presenting higher probability of becoming frail.<sup>31</sup> However, in the present study, the condition of overweight was correlated as a protective factor against frailty, and this is supported by a review study that suggested that overweight was beneficial to elderly individuals, because of reduction of all-cause mortality.<sup>32</sup> This may be

important, given the repercussions of hospitalization and the intermediate condition of frailty that includes non-intentional weight loss. Nevertheless, some interventions directed towards elderly individuals within this setting might have influenced this result.

BMI has been shown to be an indicator for nutritional risk assessment and measurement of body fat, and is a diagnostic parameter for overweight and obesity. However, it presents some limitations, since it does not consider body composition and its distribution, which could lead to under or overestimation of body fat.<sup>32,33</sup> Another point that should be taken into consideration is sarcopenic obesity, which consists of increased levels of adipose tissue relating to the ageing process, regardless of BMI, with higher deposition of visceral fat and muscle infiltration.<sup>34</sup>

Concerning the absence of association of LDL and triglycerides with the condition of pre-frailty, another Brazilian study<sup>9</sup> also found similar results, in which LDL ( $P = 0.52$ ) and triglycerides ( $P = 0.65$ ) did not present differences. A prospective investigation in Finland<sup>35</sup> found similar percentages, without significant differences ( $P = 0.45$ ) in triglyceride and frailty levels. However, in a British prospective study, the triglyceride levels were higher among frail (12%) and pre-frail individuals (9%) than among non-frail individuals (7%), which disagrees with the results from the present study.<sup>7</sup> In another study among elderly individuals, slight or moderate elevations in triglyceride and LDL levels were observed.<sup>19</sup> Consequently, occurrences of lipid problems, among others, are risk factors for arterial coronary disease,<sup>36</sup> which is related to frailty.<sup>5</sup>

The present study had some limitations:

1. the acute condition that led to hospitalization may have influenced both the diagnosis of frailty and the cardiovascular risk factors;
2. the group assessed was of limited size, given the small sample of individuals who met the inclusion criteria.

Nevertheless, the possibility of selection bias in the study was minimized, since only the subjects who met these criteria were included. Therefore, in view of these limitations, further research should be carried out with the aim of expanding the sample size and including morbidities as potential confounders.

## CONCLUSION

The prevalence of pre-frail status was 51.7%, while 26.3% of the elderly individuals studied presented a frail condition. Regarding the cardiovascular risk factors associated with frailty syndrome, only overweight remained significantly and inversely associated with pre-frailty status in the final model.

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# Factor structure and psychometric properties of the Connor-Davidson resilience scale among Brazilian adult patients

## Estrutura fatorial e propriedades psicométricas da Escala de Resiliência de Connor-Davidson para pacientes brasileiros adultos

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### KEY WORDS:

Resilience, psychological.  
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### PALAVRAS-CHAVE:

Resiliência psicológica.  
Comparação transcultural.  
Estudos de validação.  
Psicometria.  
Questionários.

### ABSTRACT

**CONTEXT AND OBJECTIVE:** Personal resilience is associated with several mental health outcomes. The Connor-Davidson resilience scale (CD-RISC) is a widely used self-report measurement of resilience. This study aimed to investigate the reliability and validity of a Brazilian Portuguese version of the CD-RISC.

**DESIGN AND SETTING:** Cross-sectional validation study carried out in the outpatient clinics of a public university hospital.

**METHODS:** The cross-cultural adaptation followed established guidelines and involved interviews with 65 adults in psychiatric and non-psychiatric outpatient clinics at a teaching hospital. Validation was assessed through concurrent application of the Lipp Brazilian Stress Symptom Inventory (ISSL), Self-Report Questionnaire (SRQ), Sheehan Disability Scales (SDS) and Chronic Pain Grade (CPG) to 575 patients at the same setting. Temporal stability was verified through a second application to 123 participants.

**RESULTS:** Factor analysis identified four factors, named **tenacity, adaptability-tolerance, reliance on support from outside** and **intuition**. The alpha coefficient of 0.93 and intraclass correlation coefficient of 0.84 indicated good internal consistency and temporal stability. Significant correlations between this version of the CD-RISC and the ISSL, SRQ, SDS and CPG were noted. The patients at the outpatient clinic for borderline personality had resilience scores that were significantly lower than those of the patients at the general anxiety or post-traumatic stress outpatient clinics.

**CONCLUSION:** This Brazilian Portuguese version of the Connor-Davidson resilience scale exhibited adequate reliability and validity among a sample of Brazilian adult patients.

### RESUMO

**CONTEXTO E OBJETIVO:** A resiliência pessoal está associada a diversos desfechos em saúde mental. A escala de resiliência de Connor-Davidson (CD-RISC) vem sendo amplamente empregada como uma medida autorrelatada de resiliência. Este estudo teve por objetivo verificar a confiabilidade e a validade de uma versão da CD-RISC para o português no contexto cultural brasileiro.

**DESENHO E LOCAL:** Estudo transversal de validação conduzido nos ambulatórios de hospital público universitário.

**MÉTODOS:** De acordo com diretrizes bem conhecidas, a adaptação cultural foi feita com 65 adultos entrevistados em ambulatórios psiquiátricos e não psiquiátricos de um hospital de ensino. A validação se deu pela aplicação concorrente do Inventário de Stress para Adultos de Lipp (ISSL), Questionário de Autorrelato de Sintomas (SRQ), Escalas de Incapacidade de Sheehan (SDS) e Escala Graduada de Dor Crônica (CPG) a 575 pacientes do mesmo hospital. A estabilidade temporal foi verificada numa segunda aplicação a 123 participantes.

**RESULTADOS:** A análise fatorial identificou quatro fatores, nomeados como **tenacidade, adaptabilidade-tolerância, amparo e intuição**. Um coeficiente alfa de 0,93 e um coeficiente de correlação intraclass de 0,84 indicaram adequadas consistência interna e estabilidade temporal. Correlações significativas entre esta versão da CD-RISC e o ISSL, SRQ, SDS e CPG foram identificadas. Os pacientes do ambulatório para personalidade *borderline* tiveram escores de resiliência significativamente mais baixos que os pacientes dos ambulatórios geral de ansiedade ou de estresse pós-traumático.

**CONCLUSÃO:** A presente versão em português da escala de resiliência de Connor-Davidson apresentou confiabilidade e validade adequadas numa amostra de pacientes brasileiros adultos.

## INTRODUCTION

Resilience is a construct associated with the ability to adapt when challenged by stressors or adversities, or to strive despite the toughness of circumstances that are experienced.<sup>1,2</sup> The concept is rooted in other fields of science (physics, engineering and dentistry) where it relates to the resistance of materials.<sup>3</sup> Resilient materials are flexibly capable of non-permanent deformation, a property that allows them to accumulate energy and thus avoid breakage under mechanical stress. Likewise, resilient individuals (or communities) are able to adjust rapidly to the adversities of life, thus remaining on the path of wellness. Since this allegorical translation of the term resilience as a psychological construct was first made, some features usually displayed by resilient people have been reported: realistic optimism, highly positive emotionality, sense of purpose in life, an internal framework of beliefs about right and wrong, spirituality, use of active coping strategies such as problem solving and planning, ability to find meaning even in traumatic experiences, and the tendency to perceive stressful events in less threatening ways and to reframe adverse experiences in a more positive light.<sup>4,5</sup>

Although seminal authors in the field of psychological resilience have mainly investigated children under unfavorable conditions (e.g. poverty or chronic maltreatment), more recent papers have also focused on (a) traumatic experiences of both children and adults and their outcomes and (b) the interrelationships between resilience and chronic stressors.<sup>6,7</sup> Among chronic stressors, attention has been paid to people enduring chronic illnesses and ailments.<sup>8-11</sup> In a country like Brazil where the population is rapidly growing older, the resilience of people facing chronic diseases and associated limitations does matter.<sup>12</sup>

There has been notable interest in developing assessment tools for measuring individual resilience. In a review, Ahern et al. identified six measurements of resilience.<sup>13</sup> Five years later, a review by Windle et al. analyzed 15 measurements.<sup>14</sup> In the latter, instruments were ranked according to several of their attributes (consistency, length of fit, etc.), and the Connor-Davidson Resilience Scale (CD-RISC) was one of the top-ranked instruments.<sup>15</sup>

## OBJECTIVE

The objective of the present study was to investigate the reliability, validity and factor structure of a culturally adapted Brazilian Portuguese version of the Connor-Davidson Resilience Scale, in a sample of adult outpatients.

## METHODS

The protocol for this study was approved by the Institutional Review Board of the teaching hospital of a public university medical school. Cultural adaptation procedures were conducted in accordance with the guidelines proposed by Beaton et al. and Guillemin.<sup>16,17</sup>

## Connor-Davidson Resilience Scale (CD-RISC)

The CD-RISC<sup>15</sup> is a 25-item questionnaire for evaluating individual resilience. Its reliability and validity have been studied in populations in North America,<sup>15,18</sup> Europe,<sup>19-21</sup> Africa<sup>22</sup> and Asia.<sup>23-26</sup> Respondents rate items on a scale from 0 (“not true at all”) to 4 (“true nearly all the time”). The original study on the development of the CD-RISC in the general population and in patient samples provided support for the internal consistency, test-retest reliability and validity of this scale.

## Participants

For the cross-cultural adaptation phase, 65 adult patients (18 years or older) were approached in the waiting rooms of either the general outpatient clinic for anxiety disorders or the outpatient clinic for pre-anesthetic consultations for elective surgeries of the medical school's teaching hospital. For the validation phase, patients in the waiting rooms of the outpatient clinics for borderline personality disorder, post-traumatic stress disorder and chronic pain, and adult companions of pre-anesthetic consultation patients, were also approached. If these individuals presented reading and hearing disabilities or cognitive impairment, the interview was halted and the individual was excluded from the study (exclusion criteria of the study protocol). Psychiatric patients were interviewed only after the consultant psychiatrist had stated that the patient's diagnosis was among those pre-specified in the inclusion criteria of the study protocol (borderline personality, post-traumatic stress disorder or other anxiety disorder). All the participants signed an informed consent statement before the interview was started.

## Cross-cultural adaptation phase

For the cultural adaptation phase, two specialists in English-Portuguese translations (of whom one was a specialist in adult literacy in Portuguese) independently prepared Portuguese versions of the CD-RISC. A synthesis between the two versions was obtained through consensus agreement between the translators. A cultural adaptation committee (CAC) was then created, including both of the specialists in English-Portuguese translations, a psychologist, a psychiatrist, an epidemiologist and a physical medicine and rehabilitation doctor. The comprehension of the Portuguese version was verified through interviews with subjects within the target population, during which the respondents were asked about their understanding of each question and invited to offer suggestions for words or expressions that might clarify their meaning. At three successive meetings, the cultural adaptation committee discussed the ongoing results from the interviews and suggested changes to the Portuguese version, with the aim of improving comprehension while maintaining equivalence with the original instrument. The final version was defined after 60 patients had been interviewed.

Two independent back-translations of the final version were made by native English-speaking professional translators, and a synthesis was agreed upon through reaching a consensus. The authors of the original instrument were contacted, and agreed that conceptual equivalence had been maintained between the back-translation and the original instrument. One of the authors proposed a minor alteration to item 6. After this item had been altered, five additional interviews were conducted to test the adequacy of the modification. The final version was then named the Connor-Davidson Resilience Scale Brazil (RISC-Br). Figure 1 presents a flowchart of the cross-cultural adaptation process.

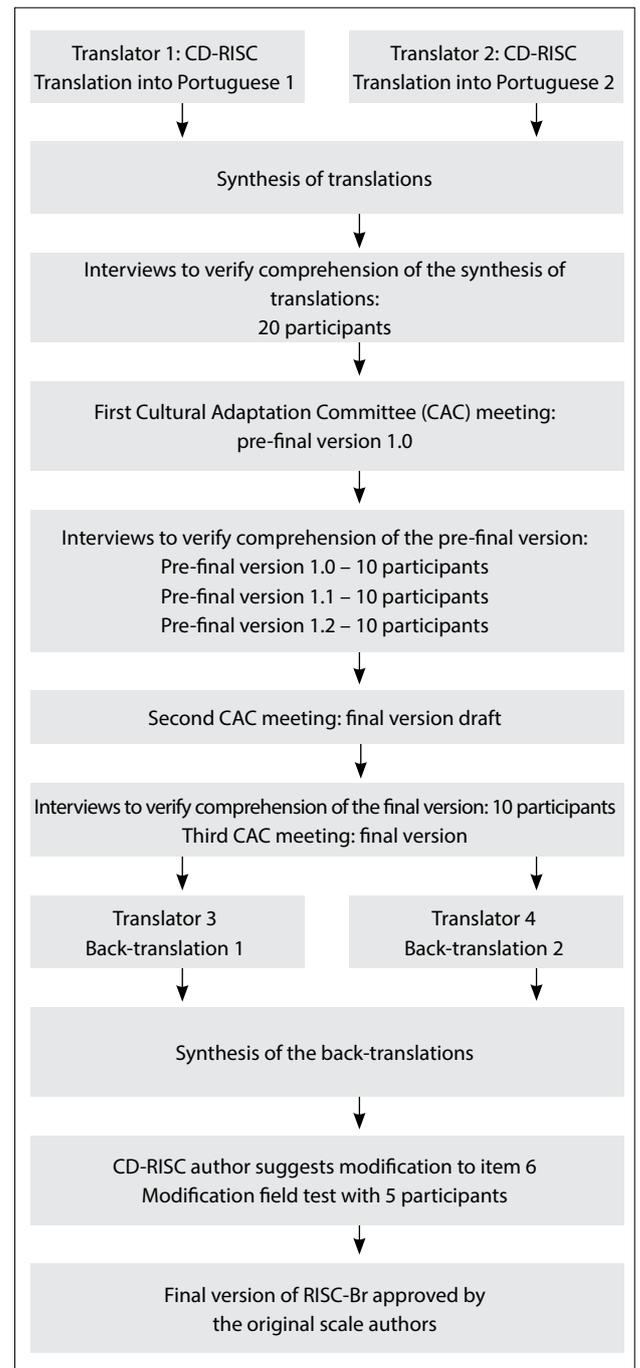
### Validation phase

The validation assessments used included concurrent application of the RISC-Br, the Lipp Brazilian Stress Symptom Inventory,<sup>27</sup> the Brazilian version of the Self-Report Questionnaire,<sup>28</sup> the Sheehan Disability Scale<sup>29</sup> and the Brazilian version of the Chronic Pain Grade<sup>30</sup> to 575 participants who were attending the hospital's outpatient clinics. We expected to find an inverse relationship between resilience and distressing symptoms as measured using the Brazilian Lipp Stress Symptom Inventory, Self-Report Questionnaire and the pain intensity subscale of the Chronic Pain Grade, as well as between resilience and the self-reported negative impact of such symptoms as measured using the Sheehan Disability Scale and the two subscales of activity limitation due to pain in the Chronic Pain Grade. In other words, lower resilience was expected to be associated with higher scores in these instruments. We also expected that patients enduring chronic pain would probably display greater resilience, and that borderline patients would have the lowest resilience scores. Test-retest reliability was studied by means of a second interview, which was conducted between 7 and 14 days after the first encounter.

### Data analysis

The demographic and clinical characteristics of the sample were established through descriptive analysis. Exploratory factor analysis was performed on the data from the validation phase ( $n = 575$ ). In accordance with Kaiser's rule, principal components with eigenvalues greater than 1.0 were selected for oblique (direct oblimin) rotation. Oblique rotation is preferable when the construct under exploration is expected to have dimensions (factors) that relate to each other.<sup>31</sup> Exploratory factor analysis yielded four factors accounting for more than 55% of the variance of the scale. Cronbach's alpha coefficient was used to assess internal consistency for each factor and for the whole scale. Intraclass correlation coefficients were calculated in order to assess the test-retest reliability using a subsample of the interviewees who were contacted on a second occasion ( $n = 123$ ). Spearman coefficient correlations were used to assess construct validity. Thirteen items

were used as comparison criteria: the six subscales of the Brazilian Lipp Stress Symptom Inventory, the Self-Report Questionnaire, the three subscales of the Sheehan Disability Scale and three subscales of the Chronic Pain Grade. Although not pertaining to the formal objective of the study, the mean resilience scores from the six subsamples of the validation phase were tested for differences by means of analysis of variance (ANOVA).



**Figure 1.** Cross-cultural adaptation process for the Brazilian version of the Connor-Davidson Resilience Scale.

## RESULTS

### Descriptive statistics

The majority of the participants were women (428; 74%), with an average age of 44 years (range: 18-81) and 10 years of formal schooling. The participants were predominantly married (56%) and of socioeconomic levels B or C (92%), on a scale from A to E. Table 1 shows the sample distribution according to sociodemographic characteristics.

**Table 1.** Demographic characteristics of participants in the Connor-Davidson Resilience Scale Brazil (RISC-Br) validation phase

	N	%
Age		
18 25	50	8.7
25 35	112	19.5
35 45	139	24.2
45 55	153	26.6
55 65	83	14.4
> 65	38	6.6
Sex		
Female	428	74.4
Male	147	25.6
Years of formal schooling		
0-3	10	1.7
4-7	112	19.5
8-10	88	15.3
11-15	365	63.5
Self-rated ability to read		
Can read very well	186	32.3
Can read well	262	45.6
Can read reasonably well	116	20.2
Can read poorly	11	1.9
Group (subsamples)		
(1) Pre-anesthetic consultation	129	22.4
(2) Chronic pain	120	20.9
(3) Anxiety - general	96	16.7
(4) Anxiety - PTSD	44	7.7
(5) BPD	42	7.3
(6) Group (1) patients' companions	144	25.0

PTSD = post-traumatic stress disorder; BPD = borderline personality disorder.

### Factor structure and reliability

Principal component analysis yielded four components, with eigenvalues of 10.2, 1.5, 1.2 and 1.1. These values accounted for 40.8, 5.8, 4.7 and 4.3% of the total variance, respectively. Oblique rotation was calculated using this four-factor solution, and the resulting factors were named **tenacity** (items 5, 10-12, 15, 16 and 21-25), **adaptability-tolerance** (1, 4, 6-8, 14 and 17-19), **reliance on support from outside** (2, 3 and 13) and **intuition** (9 and 20) (Table 2).

Cronbach's alpha coefficient was 0.91 for factor 1, 0.86 for factor 2, 0.57 for factor 3, 0.49 for factor 4 and 0.93 for the complete scale. The RISC-Br was completed on a second occasion by 123 participants, after an interval of 7-14 days (median: 10 days). Intraclass correlation coefficient was 0.84 for factors 1 and 2, 0.72 for factor 3, 0.55 for factor 4 and 0.86 for the complete scale (Table 2).

### Construct validity

Spearman correlations were calculated between the RISC-Br and the six subscales of the Brazilian Lipp Stress Symptom Inventory, the Self-Report Questionnaire, the three subscales of the Sheehan Disability Scale and three subscales of the Chronic Pain Grade. Correlations were also calculated between each of these items and each of the four factors of the RISC-Br (Table 3). Significant negative correlations were observed with all but one of the six subscales of the Brazilian Lipp Stress Symptom Inventory, with the Self-Report Questionnaire and with the subscales of the Sheehan Disability Scale. The Spearman correlation coefficients ranged from negative 0.45 to negative 0.26 ( $P < 0.01$ ). Overall, the correlations were stronger for Factors 1 and 2 and weaker for 3 and 4. Stronger correlations were observed with the psychological than with the physical dimensions of stress symptoms of the Brazilian Lipp Stress Symptom Inventory. Among the three dimensions of the Sheehan Disability Scale, social impairment showed the strongest correlation with the RISC-Br. No correlation was found between the RISC-Br (or its factors) and the dimension of psychological stress symptoms over the last 24 hours in the Brazilian Lipp Stress Symptom Inventory. Among the dimensions of the Chronic Pain Grade, there were significant, although modest, negative correlations between pain intensity and Factor 3, and between pain-related disability and Factor 2 (-0.19 in both cases;  $P < 0.05$ ).

**Table 2.** Connor-Davidson Resilience Scale Brazil (RISC-Br) factor structure with items associated with each factor

	Eigenvalue	% of variance explained	Alpha	ICC	Items
RISC-Br		100.0	0.93	0.86	
Factor 1: Tenacity	10.2	40.8	0.91	0.84	5, 10-12, 15, 16, 21-25
Factor 2: Adaptability-tolerance	1.5	5.8	0.86	0.84	1, 4, 6-8, 14, 17-19
Factor 3: Reliance on support from outside	1.2	4.7	0.57	0.72	2, 3, 13
Factor 4: Intuition	1.1	4.3	0.49	0.55	9, 20

ICC = intraclass correlation coefficient.

**Table 3.** Spearman correlations between the Connor-Davidson Resilience Scale Brazil (RISC-Br), its factors and the external comparison variables

	RISC-Br	Factor 1	Factor 2	Factor 3	Factor 4
RISC-Br	1				
Factor 1	0.929*				
Factor 2	0.922*	0.766*			
Factor 3	0.568*	0.484*	0.395*		
Factor 4	0.610*	0.514*	0.497*	0.343*	
Lipp-wb	-0.258*	-0.242*	-0.275*	-0.090 <sup>†</sup>	-0.108 <sup>†</sup>
Lipp-wp	-0.356*	-0.351*	-0.361*	-0.151*	-0.127*
Lipp-mb	-0.271*	-0.255*	-0.280*	-0.107 <sup>†</sup>	-0.105 <sup>†</sup>
Lipp-mp	-0.436*	-0.405*	-0.449*	-0.192*	-0.186*
Lipp-db	-0.275*	-0.260*	-0.287*	-0.102 <sup>†</sup>	-0.129*
Lipp-dp	-0.014	0.019	-0.027	-0.016	-0.010
SRQ	-0.447*	-0.426*	-0.455*	-0.183*	-0.202*
Sheehan-f	-0.319*	-0.311*	-0.312*	-0.175*	-0.119*
Sheehan-w	-0.330*	-0.334*	-0.319*	-0.129*	-0.147*
Sheehan-s	-0.372*	-0.368*	-0.356*	-0.171*	-0.170*
CPG-i	-0.169	-0.118	-0.159	-0.189 <sup>†</sup>	-0.157
CPG-l	-0.130	-0.023	-0.187 <sup>†</sup>	-0.143	-0.048
CPG-d	0.022	0.088	-0.027	-0.023	-0.075

\*P < 0.01; <sup>†</sup>P < 0.05.

wb = body symptoms of last week; wp = psychological symptoms of last week; mb = body symptoms of last month; mp = psychological symptoms of last month; db = body symptoms of last day; dp = psychological symptoms of last day; SRQ = Self-Reporting Questionnaire; Sheehan-f = symptoms affect family relations; Sheehan-w = symptoms affect work activities; Sheehan-s = symptoms affect social/leisure activities; CPG-i = pain intensity; CPG-l = activity limitation due to pain; CPG-d = days of limitation.

## DISCUSSION

This paper reports on the cross-cultural adaptation and validation of a Brazilian Portuguese version of the CD-RISC, using selected clinical samples. The RISC-Br showed adequate reliability and validity. A four-factor solution seemed to fit well with the theoretical framework of resilience, and significant correlations with comparison criteria were observed.

Psychometric comparisons between versions of the CD-RISC across cultures should be made cautiously. Beyond the cultural differences, there have been discrepancies in the rotation method (orthogonal or oblique), ages of participants, strategies for questionnaire delivery (from internet-based data-gathering to personal one-to-one interviews) and sources of the samples (population-based, clinical samples, subgroups affected by a specific catastrophic event and so forth).

Differing from the original CD-RISC (which was presented with five factors and varimax rotation), a four-factor solution emerged from the RISC-Br, in accordance with Kaiser's rule, using either varimax or oblimin rotation. We preferred to analyze the results from oblique rotation, since the domains of the resilience

construct were expected to relate to each other.<sup>31</sup> Furthermore, since the factor structure of the CD-RISC was studied in a community-based sample and that of the RISC-Br in a clinical sample, strict comparison may not be appropriate. Indeed, some investigators have challenged the five-factor solution of the original scale. Campbell-Sills and Stein reported that a four-factor solution was the best fit, in testing the scale using two samples of American undergraduates (around 500 students in each sample). One of these four factors contained items with disparate themes (social support and purpose in life), which led the authors to attempt to refine the scale through dropping several of its items.<sup>18</sup> In the Turkish validation study, even though five factors were identified, the author reported that the item-factor loadings were dissimilar from those of the original scale.<sup>19</sup> Furthermore, from the validation studies in China, a three-factor structure emerged from an adult sample,<sup>26</sup> and was confirmed using adolescents.<sup>24</sup> A study on South African adolescents also failed to confirm the original five-factor structure of the CD-RISC.<sup>22</sup>

This four-factor solution for the RISC-Br seems to have discarded the spirituality domain of the original scale (which was its fifth factor). The two items that were assumed to relate to spirituality in the original scale (item 3, "Fate or God can help"; and item 9, "Good or bad, most things happen for a reason") loaded differently but very coherently in the RISC-Br. The former loaded most strongly in the factor of **reliance on support from outside**, which also harbored item 2 ("I've a secure relationship that helps me") and item 13 ("In times of stress I know where to turn for help"). It is likely that, whether from God or from an acquaintance in the neighborhood, these two items resonated as indistinguishable forms of help from outside in the context of the present sample. Item 9 loaded most strongly in the factor of **intuition**, where item 20 was also placed ("sometimes you have to act on a hunch, without knowing why"). In these two items of factor 4, there is an intuitive feeling of safeness despite uncertainty. It is noteworthy that in the original study, both items (3 and 9) of the fifth factor ("**influences of spirituality**") were considered to be somewhat problematic because they displayed cross-factor loadings and low item-total score correlations.<sup>15</sup> The same was observed in an Australian study<sup>32</sup> and among the Chinese population (in this last case, possibly attributable to differences in religious beliefs).<sup>24</sup>

The alpha coefficient of 0.93 that was obtained for the RISC-Br demonstrates that it had good internal consistency, although there is evidence of a certain degree of content redundancy. Redundancy across the scale items has also been noted by authors from other cultural contexts. The two core factors of **tenacity** and **adaptability-tolerance** exhibit excellent alpha coefficients, while the modest coefficients of the factors of **reliance on external support** and **intuition** can be attributed to the subscale

shortness (three and two items respectively). The adequate intra-class correlation coefficients indicated that there was good temporal stability both for the entire RISC-Br and for its subscales.

As expected, the resilience scores correlated negatively with the Self-Report Questionnaire, the Sheehan Disability Scale and the majority of the dimensions of the Brazilian Lipp Stress Symptom Inventory. The lack of correlation between the RISC-Br and the dimension of psychological symptoms over the last 24 hours in the Brazilian Lipp Stress Symptom Inventory can be attributed to the fact that this dimension only comprises three items, which had antagonistic values in relation to the items of the other dimensions. These three items invoke “positive” feelings (“sudden urge to start new projects; excitement; increased motivation”) instead of “negative” distressing symptoms (“dry mouth; dizziness; tiredness”).

This study failed to demonstrate a consistent correlation between chronic pain and resilience, with only two weak correlations arising from two factors of the RISC-Br and two dimensions of the Chronic Pain Grade. Nevertheless, the Chronic Pain Grade showed appropriate psychometrics in its validation study.<sup>30</sup> It is reasonable to hypothesize that in our sample of chronic pain outpatients, a response artifact may have biased the participants’ answers towards endorsing high levels of symptoms, regardless of their inner resilience, since this would assure them of continuity of care in the public specialized pain clinic. In the Chronic Pain Grade validation study, data on chronic pain was collected from the community.

This study did not aim to test hypotheses. At best, some hypotheses arose. Many authors indicated that personal resilience was a predictor of mental health, and that low resilience was associated with several psychiatric conditions (particularly anxiety disorders).<sup>33-35</sup> Within our subsamples, psychiatric patients indeed presented significantly lower resilience scores than those of non-psychiatric patients. There are many recent studies in the psychiatric literature regarding the resilience of post-traumatic stress disorder patients,<sup>5</sup> and (to our knowledge) none on the resilience of borderline patients. Borderline patients also need to become a paradigmatic source of information regarding the development of personal resilience.

This study presents limitations. First, it was not a population-based study. The absence of a sample from the community precludes any inference about the resilience of Brazilian general population. Second, the psychometrics of two factors (**social support** and **intuition**) did not reach good levels. This may have occurred because of the paucity of items devoted to these domains. In this preliminary appraisal on how the RISC-Br would perform within specific clinical samples, we intended to explore its original structure. In further research, confirmatory factor analysis will provide scale refinement, probably through

dropping some items. Third, no rigid criteria for recruiting participants were adopted. Nevertheless, the study subsamples were all derived from the same population (clients of the same hospital), which may, to some degree, have restricted the influence of selection bias.

## CONCLUSION

The objective of making an instrument available for measuring personal resilience in Brazil was attained. The RISC-Br showed adequate reliability, temporal stability and construct validity when tested in clinical settings on adult psychiatric and non-psychiatric patients. In the Brazilian version, the 25 scale items clustered within four factors, but the comprehensibility of the factors within a conceptual framework of resilience seems to have been maximized in accordance with the Brazilian cultural context.

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# Translation to Brazilian Portuguese, cultural adaptation and reproducibility of the questionnaire “Ankylosing Spondylitis: What do you know?”

Tradução para a língua portuguesa brasileira, adaptação cultural e reprodutibilidade do questionário “Ankylosing Spondylitis: What do you know?”

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## KEY WORDS:

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## PALAVRAS-CHAVE:

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Conhecimento.  
Tradução.  
Educação.  
Inquéritos e questionários.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Ankylosing spondylitis (AS) generates inflammation and pain in entheses, peripheral joints and the spine. Education regarding AS can improve patients' disability. Thus, it is important to assess patients' knowledge. There is no instrument in the literature for assessing knowledge of AS in Portuguese. The aim here was to translate to the Brazilian Portuguese language, culturally adapt and test the reliability of the questionnaire “Ankylosing Spondylitis: What do you know?” and to correlate the findings with other factors.

**DESIGN AND SETTING:** Original article regarding validation of questionnaire, produced at the Federal University of Sao Paulo (Unifesp).

**METHODS:** For translation and cultural adaptation, Guilleman methodology was used. After the first phase, the reliability was tested on 30 patients. Correlations between these scores and other factors were examined.

**RESULTS:** In the interobserver assessment, the Pearson correlation coefficient and Cronbach's alpha were 0.831 and 0.895, respectively. In the intraobserver evaluation, the intraclass correlation coefficient and Cronbach's alpha were 0.79 and 0.883, respectively. At this stage, the score for area of knowledge A showed correlations with ethnicity and education; the score for area D, with age; the total score and scores for areas A and B with “social aspects” of SF-36; and the score for area D with “pain,” “vitality” and “emotional aspects” of SF-36.

**CONCLUSION:** The Brazilian version of the questionnaire “Ankylosing Spondylitis: What do you know?” was created. It is reproducible and correlates with education level, ethnicity and the SF-36 domains “social aspects” and “emotional aspects”.

## RESUMO

**CONTEXTO E OBJETIVO:** A espondilite anquilosante (EA) gera inflamação e dor em enteses, articulações periféricas e coluna vertebral. A educação na EA pode melhorar a incapacidade dos pacientes. Assim, é importante avaliar o conhecimento do paciente. Não há na literatura instrumento que avalie o conhecimento da EA na língua portuguesa. O objetivo foi traduzir para a língua portuguesa brasileira, realizar a adaptação cultural e testar a confiabilidade do questionário Ankylosing Spondylitis: What do you know? e relacionar os resultados com outros fatores.

**TIPO DE ESTUDO E LOCAL:** Artigo original de validação de questionário realizado na Universidade Federal de São Paulo (Unifesp).

**MÉTODOS:** Para tradução e adaptação cultural, foi utilizada a metodologia de Guilleman. Depois da primeira fase, a confiabilidade foi testada em 30 pacientes. Correlações entre esses escores e outros fatores foram avaliadas.

**RESULTADOS:** Na avaliação interobservador, o coeficiente de correlação de Pearson e o alpha de Cronbach foram de 0,831 e 0,895, respectivamente. Na avaliação intra-observador, o coeficiente de correlação intraclasse e o alpha de Cronbach foram de 0,79 e 0,883, respectivamente. Nesta etapa, foram encontradas correlações entre etnia e escolaridade e a área de conhecimento A, e entre idade e a área D; entre o escore total e escores das áreas A e B e “aspectos sociais” do SF-36 e entre a área D e “dor”, “vitalidade” e “aspectos emocionais” do SF-36.

**CONCLUSÃO:** Foi criada a versão brasileira do questionário “Ankylosing Spondylitis: What do you know?”, que é reprodutível e se correlaciona com escolaridade, etnia e os domínios “aspectos sociais” e “aspectos emocionais” do SF-36.

## INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the spine. It may progress to morning stiffness and progressive functional limitation of the axial skeleton, and may also lead to peripheral involvement. It usually starts in young adults, mostly white males and human leucocyte antigen-B27 (HLA-B27)-positive individuals.<sup>1</sup>

An epidemiological study conducted in all regions of Brazil showed that out of 1036 patients with spondyloarthritis, 72.3% were diagnosed with ankylosing spondylitis, 13.7% psoriatic arthritis, 6.3% undifferentiated spondyloarthropathy, 3.6% reactive arthritis, 3.1% juvenile spondyloarthropathy and 1% arthritis relating to inflammatory bowel disease. Additionally, 73.6% of the patients were men. With regard to ethnicity, 59.5% were white, 5.2% black, 20.7% mixed race and 14.6% other ethnicities, such as brown and Asian. Axial disease was observed in 36.7% and axial involvement associated with peripheral and entheses joints in 7.9%.<sup>2</sup>

Like in many other rheumatic diseases, the social and medical costs are high. Indirect costs associated with days of missed work and lost productivity are the highest element of these costs, due to the large functional limitations caused by the disease.<sup>3</sup>

The Modified New York Criteria are most commonly used for confirmation of a diagnosis of AS. These combine clinical and radiographic criteria.<sup>4</sup>

Educational interventions and their implications regarding patients' knowledge, self-efficacy, preparation and coping in relation to their illness have been studied and closely correlated with treatments for serious diseases such as cancer.<sup>5</sup> Regarding multiple sclerosis, improved self-efficacy has been more closely correlated with better quality of life than has physical activity.<sup>6</sup> It is believed that such relationships are also strong in connection with other diseases, such as AS.

Education for patients with inflammatory arthritis is highly recommended by the European League against Rheumatism (EULAR). This organization recently developed a consensus through analysis of the literature and experts' opinions.<sup>7</sup>

One method of evaluating the efficacy of an educational program consists of measuring the modification of the patient's knowledge.<sup>8</sup> Lubrano et al. created an AS knowledge questionnaire that they named "Ankylosing Spondylitis: What do you know?" (ASWK),<sup>9</sup> which was later on validated among 62 patients in the United Kingdom (UK). The questions were created by consulting four rheumatologists, a physiotherapist, an occupational therapist and two research nurses. The instrument contains 14 questions, with 72 possible answers, among which only 25 are correct. It is divided into four areas of knowledge:

1. general knowledge, etiology, symptoms and blood tests;
2. immunogenic test (HLA-B27) and inheritance;
3. drug treatment and physiotherapy; and
4. joint protection and energy conservation.

The final score is calculated by adding one point for each correct answer. The questionnaire was considered to be a good tool for detecting these patients' knowledge level, while even being sensitive to small changes in theoretical knowledge levels.

The questionnaire was translated into French and it was concluded that the level of patients' knowledge among the French population seemed to be inadequate.<sup>10</sup> We believe this finding may also be true for other populations worldwide.

Therefore, while implementation of an educational program for patients affected by AS is extremely important, so is validation of its efficacy. However, in the literature, there is no questionnaire for assessing knowledge among patients with AS that has been validated for use in Portuguese.

## OBJECTIVE

The aim of this study was to translate into Portuguese, culturally adapt and test the reliability of the ASWK questionnaire. In addition, we aimed to correlate the findings regarding knowledge of the disease, i.e. pain, function, disease activity and quality of life, with personal and demographic data such as gender, age, marital status, education level, profession, disease duration, time of diagnosis and medication.

## METHODS

This study was conducted in three distinct stages. Firstly, we translated the instrument into Brazilian Portuguese, taking into consideration all the necessary cultural adaptations. Secondly, we tested the reliability of the ASWK questionnaire for the Brazilian population and, thirdly, we correlated AS knowledge levels with other parameters collected from the patients.

We interviewed 60 patients who had been diagnosed with AS in accordance with the Modified New York Criteria.<sup>2</sup> These patients were of both genders and aged between 18 and 65, and they were selected at our institution's outpatient clinics.

The study was approved by our institution's Ethics Committee through the registration number CAAE-01752512.0.0000.5505. All the patients signed an informed consent statement confirming their agreement to participate in the study.

### Translation and cultural adaptation

After the original authors had authorized translation of the questionnaire, we started the process of translating and adapting the instrument, following the systematization proposed by Guillemin et al. and Beaton et al.<sup>11-13</sup>

### Translation into Portuguese

The translation was carried out by two English teachers whose first language was Portuguese and who did not know the original questionnaire, but were informed about the purpose of the study. The teachers worked independently and therefore produced two

versions of the questionnaire in Portuguese. Later on, these were compared by a multidisciplinary team consisting of one rheumatologist and two physiotherapists. The professionals examined the two versions in order to search for any discrepancies between them. They also analyzed the applicability of each question to finally obtain a single version of the translation (V1).

### Rating of the initial translation (back translation)

V1 was then translated back into English, separately by two other English teachers whose first language was English. At this stage, the translators had no knowledge about the original questionnaire or the objectives of this study.

The two new versions were compared with the original questionnaire in order to analyze the semantic equivalence, thus allowing the V1 questionnaire to be accepted as the final version in Portuguese. The final Brazilian version is called "Espondilite anquilosante: o que você sabe a respeito?" (EAVS).

### Rating of understanding of questionnaire (cultural adaptation)

The EAVS V1 questionnaire was administered to 30 patients with AS in conformity with the Modified New York Criteria.<sup>2</sup> Questions or items that were not understood by 20% or more of the patients were analyzed by the multidisciplinary group with the aim of possibly modifying them so as to maintain the original objectives of the questionnaire. All the modified questions would be applied to a new group of 30 patients to check their understanding. If necessary, the questions would again be modified until they were fully understood by 80% or more of the participants.

### Evaluation of EAVS reliability

After translation and cultural adaptation, the questionnaire was applied to a new group of 30 patients who had been diagnosed with AS, in accordance with the Modified New York Criteria,<sup>4</sup> with three evaluations.

The first two evaluations were performed consecutively on the same day by two researchers (interobserver assessment). The third evaluation was carried out 7-14 days after the initial assessment by one of the previous researchers (intraobserver assessment).

### Correlation with clinical and demographic parameters

At this stage, just after the intraobserver assessment, instead of the EAVS instrument, we applied an evaluation sheet and other questionnaires in order to gather data on patients' identification and disease characteristics. All the information collected was used to make correlations with specific AS knowledge and other parameters of the disease. We also evaluated the following:

1. **pain**, using the 10 cm Numerical Rating Scale for Pain,<sup>14</sup> which is a 10 cm scale, numbered 0-10, that patients mark according to their level of pain;
2. **functionality**, using the Bath Ankylosing Spondylitis Functional Index (BASFI),<sup>15</sup> which consists of 10 questions about AS patients' functional capacity to complete daily tasks, and the Health Assessment Questionnaire for Spondyloarthropathies (HAQS),<sup>16</sup> a questionnaire on daily activities in which patients are directed to choose between the responses "no difficulty", "some difficulty", "a great amount of difficulty" and "unable to complete task", according to their limitations;
3. **mobility**, through the Bath Ankylosing Spondylitis Metrology Index (BASMI),<sup>17</sup> which consists of five measurements: wall-tragus distance, lumbar flexion, cervical rotation, lateral lumbar flexion and intermalleolar distance; each measurement is awarded a score of: 0 (mild disease), 1 (moderate disease) or 2 (advanced disease), thus resulting in the final BASMI score of 0-10; and activity, through the bath ankylosing spondylitis disease activity index (BASDAI),<sup>15</sup> which consists of six questions relating to five symptoms from the preceding week: tiredness, joint pain, lumbar pain, morning pain and stiffness, which were evaluated using a 10 cm horizontal visual analogue scale (VAS); and finally
4. **quality of life**, by applying the Short-Form-36 (SF-36),<sup>18</sup> which evaluates the quality of life of the general population, and the Ankylosing Spondylitis Quality of Life (ASQoL),<sup>19</sup> which evaluates the quality of life of patients with AS.

In addition to making correlations using the above questionnaires, the total score and the score from each survey area were correlated with the clinical parameters of the disease and with the demographic data.

### Statistical analysis

The clinical and demographic data at the cultural adaptation and reliability stages were analyzed using descriptive statistics: mean and standard deviation for categorical variables; and frequency and percentage for numerical variables.

Reliability was evaluated by means of Student's t test. In this analysis, we used the Pearson correlation coefficient for the interobserver analysis and the intraclass correlation coefficient for the intraobserver analysis. For both analyses, we used Cronbach's alpha coefficient to analyze the internal consistency of the instrument.

In order to correlate the results from the knowledge questionnaire with the clinical and demographic parameters of the disease, we used Student's t test for categorical data, Pearson's correlation coefficient for normal numerical data and Spearman's correlation coefficient for non-normal data. To correlate the scores from the EAVS questionnaire with the data from the other questionnaires, we used Pearson's correlation coefficient.

The significance level was set at  $P < 0.05$ . The Statistical Package for the Social Sciences (SPSS) 19.0 software was used for the analysis.

## RESULTS

V1 was reviewed and modified by the multidisciplinary committee following the two initial translations in order to ensure that the content and grammar suited the Portuguese language and Brazilian culture.

Alternatives “a” and “b” of question 14 were modified by the committee. Originally, alternative “a” stated: “Parents with ankylosing spondylitis are more likely to have children with ankylosing spondylitis”; and “b”: “Parents with ankylosing spondylitis are less likely to have children with ankylosing spondylitis”. After reaching a consensus to change them so as to better match the content, the wording became, for “a”: “Parents with ankylosing spondylitis have a great chance of having children with ankylosing spondylitis”; and “b”: “Parents with ankylosing spondylitis have little chance of having children with ankylosing spondylitis”.

### Cultural adaptation

Thirty patients who had been diagnosed with AS participated in the initial stage of implementation of the EAVS questionnaire to check its cultural equivalence. No grammatical changes to V1 were needed. The final version is shown in **Appendix 1**.

**Table 1** shows the clinical and demographic data of the 30 patients diagnosed with AS who were included in the cultural adaptation phase of the Portuguese version of the questionnaire.

In correlating the total score from the EAVS questionnaire with the clinical and demographic data, we found correlations for education, using Spearman's correlation coefficient (0.444, with  $P = 0.014$ ); and for ethnicity, using Student's *t* test ( $P = 0.023$ ), such that white participants had higher scores in the questionnaire.

### Reliability

At the reliability assessment stage, the translated questionnaire was applied again to the 30 patients with AS. **Table 1** shows the clinical and demographic characteristics of these patients.

In the interobserver analysis, Pearson's correlation coefficient was  $r = 0.813$ , with  $P < 0.001$ . In the intraobserver analysis, the intraclass correlation coefficient was found to be  $r = 0.790$ , with  $P < 0.001$ . Cronbach's alpha coefficients were 0.895 and 0.883, respectively. These data are shown in **Table 2**.

From analysis on the correlation between the total score of the questionnaire and the demographic data and clinical data on the disease, we found a correlation regarding education. Spearman's correlation coefficient was 0.587, with  $P = 0.001$ , as shown in

**Table 1.** Clinical and demographic characteristics of the 30 patients included in the cultural adaptation and reliability phases

Data	Patients of cultural adaptation phase (n = 30)	Patients of reliability phase (n = 30)
Age in years – mean (SD)	47.9 ± 9.4	48.4 (9.5)
Gender – n (%)		
Male	23 (76.7)	20 (66.7)
Female	7 (23.3)	10 (33.3)
Ethnicity – n (%)		
White	19 (63.3)	19 (63.3)
Brown or black	11 (36.7)	11 (36.7)
Marital status – n (%)		
Married	21 (70)	21 (70)
Single or widowed	9 (30)	9 (30)
Education in years – mean (SD)	10 (4.6)	8.9 (5.2)
Occupation – n (%)		
Retirees due to disability	24 (80)	24 (80)
Others	6 (20)	6 (20)
Duration of symptoms in years – mean (SD)	18.2 (10.1)	21.8 (11.3)
Duration of diagnosis in years – mean (SD)	12.5 (6.8)	10.9 (7.4)
Biological medicine alone or in combination – n (%)	13 (43.3)	13 (43.3)
Scores from EAVS – mean (SD)	15.4 (2.5)	17.33 (3.47)

SD = standard deviation; EAVS = Questionnaire in Portuguese: “Espondilite anquilosante: o que você sabe a respeito?”

**Table 2.** Interobserver and intraobserver reliability

	Interobserver		Intraobserver
	First evaluation	Second evaluation	Third evaluation
Total score: mean (SD)	16.23 (2.82)	15.10 (3.02)	17.33 (3.47)
P	1.00		0.008
Correlation coefficient: r (P)	0.813 (< 0.001) <sup>1</sup>		0.790 (< 0.001) <sup>2</sup>
Cronbach's alpha coefficient	0.895		0.883

SD = standard deviation; <sup>1</sup>Pearson's correlation; <sup>2</sup>Intraclass correlation.

**Table 3.** No correlation was found between the total score and the clinical and categorical demographic data. These data are presented in **Table 4**.

**Table 3.** Correlation of the total score with the numerical clinical and demographic data in the reliability assessment phase

Age	PC	SC	P
	<b>-0.308</b>	-	<b>0.098</b>
Duration of symptoms	-0.091	-	0.633
Duration of diagnosis	-0.194	-	0.304
Education level	-	0.587	0.001

PC = Pearson's correlation coefficient; SC = Spearman's correlation coefficient.

**Table 4.** Correlation of the total score with the categorical clinical and demographic data in the reliability assessment phase

	Total score: mean (SD)	P
Gender		
Female	17 (4.64)	0.717
Male	17.5 (2.84)	
Ethnicity		
White	18 (2.98)	0.170
Brown or black	16.18 (4.07)	
Marital Status		
Married	17.62 (3.12)	0.500
Single or widowed	16.67 (4.30)	
Occupation		
Retirees due to disability	16.92 (3.54)	0.193
Others	19 (2.83)	
Biological medicine alone or in combination	17.23 (3.44)	0.890

SD = standard deviation.

Finally, the total score and the scores from areas of knowledge A ("general knowledge, etiology") and B ("immunogenic test HLA-B27") showed negative correlations with the "social aspects" domain of SF-36. Also, the score from area D ("joint protection and energy conservation") showed a negative correlation with the domains of "pain", "emotional aspects" and "vitality" of SF-36. These data and all relationships are presented in **Table 5**.

## DISCUSSION

There are a few questionnaires in Portuguese that are designed to assess patients' knowledge of certain diseases, but none of them are specific to AS. We chose to translate the ASWK<sup>5</sup> into Portuguese because it is a valid and reproducible instrument that had already been translated into another language.<sup>10</sup> The ASWK translation into Portuguese was conducted by means of internationally recommended methods.<sup>11-13</sup>

In the translation phase, the multidisciplinary committee changed two questions to better match the content of the original questionnaire. During the cultural adaptation, there was no need to change any questions, since the participants did not present any issues regarding content, as had occurred in France and the United Kingdom.<sup>9,10</sup>

In both groups, most of the patients who were evaluated had not completed high school education. We found a strong correlation between education and the level of knowledge, in the cultural adaptation and reproducibility phase. This information is important and can explain the level of knowledge presented by the participants in this study. In the cultural adaptation phase, the average EAVS score was 15.3, i.e. lower than the scores found in

**Table 5.** Correlations between the questionnaires

Questionnaires	Total score PC (P-value)	Area A PC (P-value)	Area B PC (P-value)	Area C PC (P-value)	Area D PC (P-value)
Numerical pain scale (NPS)	0.277 (0.139)	0.306 (0.100)	0.306 (0.39)	0.147 (0.437)	0.101 (0.593)
SF-36					
Functional capacity	-0.161 (0.395)	-0.063 (0.740)	0.61 (0.749)	-0.190 (0.315)	-0.251 (0.181)
Limitations on physical aspects	-0.205 (0.277)	-0.109 (0.565)	-0.135 (0.477)	-0.50 (0.793)	-0.332 (0.73)
Pain	-0.399 (0.067)	-0.252 (0.180)	-0.114 (0.550)	-0.192 (0.310)	-0.390 (0.033)
General health	-0.209 (0.269)	-0.047 (0.805)	-0.153 (0.421)	-0.219 (0.246)	-0.225 (0.232)
Vitality	-0.304 (0.103)	-0.312 (0.094)	0.183 (0.334)	-0.157 (0.408)	-0.459 (0.011)
Social aspects	-0.406 (0.026)	-0.483 (0.007)	-0.405 (0.026)	0.092 (0.627)	-0.345 (0.062)
Emotional aspects	-0.306 (0.100)	-0.296 (0.112)	-0.102 (0.591)	-0.048 (0.803)	-0.393 (0.032)
Mental health	-0.218 (0.248)	-0.341 (0.065)	0.141 (0.456)	-0.004 (0.983)	-0.278 (0.136)
BASFI	0.143 (0.452)	0.092 (0.628)	-0.100 (0.599)	0.218 (0.248)	0.139 (0.464)
BASMI	-0.063 (0.742)	-0.015 (0.936)	0.126 (0.506)	-0.091 (0.633)	-0.175 (0.354)
BASDAI	0.279 (0.135)	0.293 (0.116)	0.056 (0.768)	0.229 (0.224)	0.123 (0.517)
HAQS	0.147 (0.439)	0.015 (0.937)	-0.047 (0.806)	0.278 (0.137)	0.161 (0.396)
ASQOL	0.258 (0.168)	0.194 (0.305)	-0.019 (0.921)	0.196 (0.300)	0.318 (0.087)

PC = Pearson's correlation coefficient; Area A = general knowledge, etiology; Area B = immunogenic test HLA-B27; Area C = drug treatment and physiotherapy; Area D = joint protection and energy conservation; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BASDAI = bath ankylosing spondylitis disease activity index; HAQS = Health Assessment Questionnaire for Spondyloarthropathies; ASQOL = Ankylosing Spondylitis Quality of Life.

France and the United Kingdom, which presented 16.4 and 19.4, respectively.<sup>9,10</sup> In the reliability phase, the average was higher than in the cultural adaptation phase: 17.3.

In the UK, the patients' level of knowledge was considered high.<sup>9</sup> On the other hand, both in France and among our patients, it was low.<sup>10</sup>

For the British and French studies, the questionnaire was self-administered.<sup>9,10</sup> However, that differs from what is done in relation to most questionnaires used in Brazil, as a consequence of the major disparity in education levels attained between these countries.

In the cultural adaptation phase, we found statistically significant differences between ethnic groups regarding knowledge, and also a correlation with education in the reliability phase. The observed low level of knowledge about AS was correlated with ethnicity and educational levels, thus reflecting the educational and racial situation in Brazil.

No correlation was found between duration of the disease and knowledge of the disease, unlike what was seen in the British study, and in other studies on individuals with rheumatoid arthritis<sup>20,21</sup> and psoriatic arthritis.<sup>22</sup>

The questionnaire showed satisfactory levels of inter and intraobserver reliability, with  $r = 0.813$  and  $r = 0.790$  for the two analyses, with high correlations. It has been reported in the literature that the interobserver correlation is generally higher than the intraobserver correlation. Although the evaluations were carried out by two different interviewers, they were performed on the same day, which would explain the higher correlations in this analysis.<sup>23</sup>

To assess the patients' knowledge, the score was divided among four areas of knowledge, as it is in the original questionnaire. Area A referred to general knowledge, etiology, symptoms and blood tests; area B to immunogenic testing (B27) and inheritance; area C to drug treatment and physiotherapy; and area D to joint protection and energy conservation. There were low scores, but in three of the four areas, the average score was greater than 50% of the score for the total area. The exception was area B, which had a mean of  $0.97 \pm 0.85$ , with a maximum score for the area of 3 points. In the United Kingdom, the same area averaged  $2.63 \pm 0.52$ .<sup>5</sup>

During application of the questionnaire, it was observed that the patients who correctly answered that the antigen related to AS remembered they had already done this test for the diagnosis, but did not know that the antigen related to the disease. A small proportion correctly answered questions about genetic inheritance, but it was found that this question gave rise to the greatest number of doubts among the patients. Most of the patients believed that children had very high chances of also presenting the disease, and marked this alternative as correct. This

area was the only one to present zero scores, and it was associated with a small range of values from zero to three. These were the most difficult questions in the questionnaire, and they asked for information that patients rarely receive, either from doctors or from physiotherapists. The average percentage of correct answers in this area was therefore very small: only  $32.2\% \pm 28.3$ . The other areas showed average percentages of correct answers greater than 60%.

Area of knowledge A included general knowledge questions, etiology, symptoms and blood tests. The average percentage found was  $64.6\% \pm 21.3$ , and the mean score was  $5.17 \pm 1.70$ , with a range between 2 and 8. In the British survey, the mean was  $7.23 \pm 0.73$ , and the minimum score was 5.

Area C included questions about drug treatment and physiotherapy. Most of the patients included in this study had already undergone physiotherapy or had participated in other previous studies on physical activity in relation to AS. As a consequence, the majority of the patients correctly answered the questions about the most appropriate type of physical activity for AS. We also obtained 100% correct answers to the question about the importance of exercise. In the British survey, the mean score was  $8.81 \pm 0.54$ , with a minimum score of 7. In France, 64% of the patients achieved 100% in this area, which was the highest percentage of patients who responded correctly, thus also showing a high level of knowledge in this area. Correlations between this area and other questionnaires were found.

Finally, for area D, which included issues relating to joint protection and energy conservation, the average score was  $3.43 \pm 1.04$ , with a minimum of 1 and maximum of 5. The average percentage of correct answers was  $68.7\% \pm 20.8$ . In the British survey, the mean score was  $4.74 \pm 0.57$ . The average number of correct answers for this area of knowledge was reasonable, although a higher level of knowledge had been expected. Guidance of this nature is given both by physicians and by physiotherapists. In clinical practice, it was commonly observed that before receiving guidance on joint protection, patients had already adopted careful usage, given that after perceiving that certain ways of doing their daily and work activities led to increased or decreased pain, they began to perform these activities in different ways. Thus, the findings on the relationship between this area of knowledge and other questionnaires could be explained, in which we observed negative correlations with the domains of "pain", "vitality" and "emotional aspects" of the SF-36 questionnaire. We could conclude that patients with lower scores in these domains, which means greater impairment, had higher levels of knowledge in this area.

In this study, and in the UK study, one important factor that needs to be borne in mind was that in order to answer each question, the patients considered what was most important in their

experience with the disease and what was being asked about what they believed was the correct answer. For example, in question 2, there are two correct alternatives: "It is an inflammation in the joints of the spine" and "In some cases, the first complaint may not be in the lumbar region." Many patients believed that the alternative "Worsening in the cold weather" was also correct, since, although this is not a rule, most of them felt that their symptoms worsened in cold weather. Furthermore, patients with recent diagnoses commonly thought that "No drug is able to control the disease," was the correct alternative in Question 6, because once again, this correlated with the experience that they were going through with the medication. In question 7, patients with mild occurrences considered that the correct alternative was "Ankylosing spondylitis does not interfere in their work and physical activity," despite knowing that there are other levels of involvement in the disease. Finally, in question 11, one patient did not consider "weight" to be the alternative for a type of physical activity indicated in cases of AS, since his/her experience with muscle strengthening had led to worsening of the symptoms.

The scores from the questionnaire assessed here cannot be compared with any other tool for assessing knowledge of AS among patients with this disease because no other instruments have been translated into Portuguese for this purpose.

The translation of this questionnaire makes clear the individual need of education about the disease, facilitating the evaluation and guidance of what should be done to each patient, optimizing the conduct regarding education. Other studies, however, should be performed in order to verify the effectiveness of the evaluation, comparing the scores before and after education sessions on the disease.

## CONCLUSION

The Brazilian version of the questionnaire "Ankylosing Spondylitis: What do you know?" was created. It is reproducible and correlates with education level, ethnicity and the SF-36 domains "social aspects" and "emotional aspects".

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**Appendix 1. Brazilian Portuguese Version****Espondilite anquilosante: o que você sabe a respeito?**(Correct answers in *italics*)**1. Escolha as duas afirmações corretas na lista abaixo: espondilite anquilosante:**

- a. É uma doença infecciosa
- b. *Sua causa não é conhecida*
- c. *Ocasionalmente mais de um membro da família têm a doença*
- d. É mais comum em idosos
- e. É causada por atividade esportiva ou trauma
- f. Não sei

**2. Escolha as duas afirmações corretas na lista abaixo: espondilite anquilosante:**

- a. *É uma inflamação nas articulações da coluna vertebral*
- b. *Em alguns casos a primeira queixa pode não ser nas costas*
- c. Piora no clima frio
- d. É uma doença que tem cura
- e. Não sei

**3. Escolha as duas afirmações corretas na lista abaixo: espondilite anquilosante:**

- a. *Às vezes acomete os olhos e o calcanhar*
- b. Aumenta o risco de ataques cardíacos ou derrames
- c. *Causa dor e rigidez nas costas*
- d. Aumenta o risco de câncer
- e. Não sei

**4. Escolha os dois exames de sangue na lista abaixo que são usados para avaliar o quanto sua espondilite anquilosante está ativa:**

- a. Níveis de colesterol
- b. *VHS (velocidade de hemossedimentação)*
- c. Hemograma completo
- d. *PCR (proteína C reativa)*
- e. Não sei

**5. Escolha o exame de sangue usado para avaliar a tendência de desenvolver a espondilite anquilosante:**

- a. Ureia
- b. *HLA-B27*
- c. *HLA-DR4*
- d. Viscosidade do plasma
- e. Não sei

**6. Escolha as duas afirmações corretas na lista abaixo sobre o tratamento médico para espondilite anquilosante**

- a. *Analgésicos são úteis no alívio da dor*
- b. *Terapia medicamentosa é a única maneira de controlar a doença*
- c. Nenhum medicamento é capaz de controlar a doença
- d. *Vários anti-inflamatórios podem proporcionar uma boa noite de sono e alívio significativo da dor para que se possa praticar exercícios físicos*
- e. Não sei

**7. Escolha as duas afirmações corretas na lista abaixo:**

- a. Todos os pacientes voltarão ao normal se fizerem um programa de exercícios
- b. *Os sintomas podem aparecer e desaparecer por longos períodos*
- c. *O mais importante é manter uma boa postura*
- d. Espondilite anquilosante não interfere em seu trabalho e atividade física
- e. Não sei

**8. Escolha as duas afirmações corretas na lista abaixo no que se refere ao repouso na espondilite anquilosante:**

- a. O repouso no leito durante a maior parte do dia é a melhor opção quando suas costas estão doendo e rígidas
- b. *Quando a doença está muito ativa, talvez seja necessário um período de licença do trabalho ou internação hospitalar*
- c. Deitar de costas durante a noite toda
- d. *Deitar de bruços algum tempo antes de dormir e antes de se levantar de manhã*
- e. Não sei

Continue...

**Appendix 1. Continuation**

- 9. Escolha as duas afirmações corretas na lista abaixo sobre a cama ideal para pacientes com espondilite anquilosante**
- Qualquer cama é adequada
  - A cama deve ser firme*
  - Uma tábua de madeira debaixo do colchão é o ideal*
  - Um colchão macio é mais adequado quando as costas estão rígidas
  - Não sei
- 10. Escolha as duas afirmações corretas na lista abaixo sobre o tratamento com exercício para espondilite anquilosante**
- O exercício é uma parte importante do tratamento da espondilite anquilosante*
  - O exercício cura a espondilite anquilosante
  - O exercício enfraquece as articulações danificadas
  - Exercício regular diário é uma maneira inteligente de se manter em atividade*
  - Não sei
- 11. Escolha as duas atividades adequadas para alguém com espondilite anquilosante**
- Fazer compras
  - Natação*
  - Corrida em terreno acidentado
  - Futebol
  - Musculação*
  - Não sei
- 12. Escolha a atividade que você pode realizar quando as juntas estão doloridas e rígidas, por exemplo, durante uma crise.**
- Não fazer nenhum exercício
  - Repousar na cama durante a maior parte do dia
  - Fazer exercícios dentro dos limites que não provoquem dor*
  - Exercitar-se vigorosamente
  - Não sei
- 13. Escolha a afirmação correta na lista abaixo:**
- Manipulação da coluna vertebral pode ajudar a doença
  - Acupuntura pode curar a doença
  - Exercício na piscina pode ajudar o movimento*
  - Exercício na piscina pode piorar a doença, porque a água e a umidade podem prejudicar as articulações
  - Não sei
- 14. Escolha as duas afirmações corretas na lista abaixo que descrevem como a espondilite anquilosante pode afetar a família**
- Pais com espondilite anquilosante têm grande chance de ter filhos com espondilite anquilosante
  - Pais com espondilite anquilosante têm pequena chance de ter filhos com espondilite anquilosante*
  - O exame de sangue HLA-B27 pode indicar se os filhos do paciente com espondilite anquilosante desenvolverão a doença
  - O exame de sangue HLA-B27 não pode indicar se os filhos do paciente com espondilite anquilosante desenvolverão a doença*
  - Não sei

# Prevalence of knee arthroplasty in the state of São Paulo between 2003 and 2010

Prevalência de artroplastia de joelho no estado de São Paulo entre 2003 e 2010

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## KEY WORDS:

Knee.  
Osteoarthritis.  
Prevalence.  
Arthroplasty.  
Hospitals.

## PALAVRAS-CHAVE:

Joelho.  
Osteoartrose.  
Prevalência.  
Artroplastia.  
Hospitais.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** The volume of knee arthroplasty procedures has increased over the last decade. The aim of this study was to estimate the frequency of these procedures performed within the public healthcare system of the state of São Paulo between 2003 and 2010.

**DESIGN AND SETTING:** Cross-sectional study conducted in the state of São Paulo by researchers at Hospital do Servidor Público do Estado de São Paulo.

**METHODS:** A sample of 10,952 patients (7,891 females and 3,061 males) who underwent primary total knee arthroplasty (TKA) and revision of total knee arthroplasty (RTKA) in the state of São Paulo between 2003 and 2010 was evaluated. The patients were cataloged using the public healthcare service's TABNET software. All of the patients presented primary osteoarthritis of the knee. The variables of gender, number of primary TKA procedures and number of RTKA procedures were evaluated.

**RESULTS:** A total of 10,952 TKA procedures were performed (annual average of 1369), of which 9,271 (85%) were TKA and 1,681 (15%), RTKA. Of the TKA procedures, 72% were carried out on females ( $P < 0.0001$ ), while 70% of the RTKA procedures were on females ( $P < 0.0001$ ). The average ratio of TKA to RTKA was 5.5:1 ( $P < 0.0001$ ); the ratios in 2003 and 2010 were 9.0:1 and 4.4:1 ( $P < 0.0001$ ), respectively.

**CONCLUSION:** The number and frequency of TKA and RTKA procedures increased in the state of São Paulo between 2003 and 2010. This increase was relatively greater in RTKA than in TKA and was predominantly in female patients.

## RESUMO

**CONTEXTO E OBJETIVO:** O volume das artroplastias de joelho tem crescido na última década. O objetivo deste estudo foi estimar a frequência desses procedimentos realizados no Sistema Público de Saúde (SUS) do Estado de São Paulo no período de 2003 a 2010.

**TIPO DE ESTUDO E LOCAL:** Estudo transversal conduzido por pesquisadores do Hospital do Servidor Público Estadual.

**MÉTODOS:** Foi avaliada uma amostra de 10.952 pacientes (7.891 mulheres e 3.061 homens) submetidos a artroplastia primária total de joelho (ATJ) e a revisão de artroplastia total de joelho (RATJ) no estado de São Paulo entre 2003 e 2010. Os pacientes foram catalogados por meio do programa TABNET do SUS. Todos os pacientes eram portadores de osteoartrite primária do joelho. As variáveis analisadas foram: gênero, número de ATJs e número de RATJs.

**RESULTADOS:** No total, 10.592 ATJs foram realizadas (média anual de 1.369 procedimentos), com 9.271 (85%) ATJs e 1.691 (15%) RATJ. Das ATJ, 72% ocorreram em mulheres ( $P < 0.0001$ ), enquanto 70% das RATJs foram em mulheres ( $P < 0.0001$ ). A relação média de ATJ para RATJ foi de 5.5:1 ( $P < 0.0001$ ), com proporção em 2003 e 2010 de 9.0:1 e 4.4:1 ( $P < 0.0001$ ), respectivamente.

**CONCLUSÃO:** O número e a prevalência das ATJs e RATJs aumentaram no estado de São Paulo no período de 2003 a 2010. Essa elevação foi relativamente maior nas RATJs quando comparadas com as ATJs e ocorreu predominantemente nos pacientes do sexo feminino.

## INTRODUCTION

It has been estimated that 4% of the Brazilian population over the age of 60 years suffer from osteoarthritis (OA), and the knee is the joint that is second most commonly affected, with 37% of the cases.<sup>1</sup> The population of the state of São Paulo in 2000 was approximately 37 million inhabitants, and the population over the age of 60 represented 8.9% of this total.<sup>2</sup> By 2012, this percentage had increased to 11.5%, out of a total of 41 million people living in São Paulo.<sup>2</sup>

Over the last few decades, the rate of increase in the number of elderly people has outstripped the birthrate,<sup>3</sup> and there has been an expansion in the absolute numbers of cases of injury due to OA of the knee.<sup>4</sup> One of the therapeutic options for advanced symptomatic OA is total knee arthroplasty (TKA), which has shown a long-term success rate of 85% for relieving pain and improving function.<sup>4-10</sup> With the growth of primary TKA in absolute terms, it is reckoned that the frequency of revision TKA (RTKA) surgery will also increase.<sup>11</sup>

The growth rate of TKA surgery has tended to track the progressive aging of the population and, moreover, the recommendations relating to the operative procedure have been extended to bring in patients who, increasingly, are younger and more active.<sup>12,13</sup> On the other hand, obesity continues to increase and can be considered to be a risk factor for TKA and for complications after TKA.<sup>9,11</sup> The cost of the prosthetic implants is one of the main expenses relating to the charge of knee surgery procedures, and the average price for prosthetic knee implants continues to follow the upward trend seen over the last decade.<sup>11,14</sup>

The increasing prevalence of RTKA surgery is related to several factors. Among the most notable of these are the additions to the indications for TKA; factors associated with poor surgical technique and use of inappropriate instruments; incorrect choice of patients; the longevity of prosthetic knees; and occurrence of infection.<sup>12,13</sup> Thus, recent predictions point towards a substantial rise in the number of RTKA procedures over the next few decades.<sup>12,15</sup>

In Scandinavian countries, the increase in the number of TKA and RTKA procedures has raised the level of healthcare spending through the increased length of time for which patients are hospitalized, higher cost of implants and additional morbidity.<sup>15,16</sup> In order to better allocate financial resources and ensure efficient hospital management and implementation of economic and educational policies, it has been recommended that research should be conducted on epidemiological data relating to TKA and RTKA procedures.<sup>15-19</sup> In developing countries, few studies have assessed such data.<sup>20,21</sup>

## OBJECTIVE

The aim of this study was to estimate the frequency of knee arthroplasty procedures carried out by the public healthcare service of the state of São Paulo between 2003 and 2010.

## METHODS

This study was conducted by researchers at the Orthopedics and Traumatology Service of the Hospital do Servidor Público do Estado de São Paulo, with the approval of this institution's ethics committee (protocol no. CAAE 34035314.1.0000.5463).

Data on epidemiological assessments of knee arthroplasty procedures carried out in the whole state of São Paulo between January 2003 and December 2010 were gathered from the TABNET<sup>2</sup> and SIGTAP<sup>22</sup> databases (management systems for the table of procedures and medications and for the personnel management office of the public healthcare service). These databases are managed through the public healthcare service's hospital information system (Sistema de Informações Hospitalares/Sistema Único de Saúde, SIH/SUS) and are overseen by the Ministry of Health through the Department of Healthcare, together with state health departments and municipal health departments. The data are processed by the public healthcare service's information technology department (Departamento de Informática do Sistema Único de Saúde, DATASUS), which is part of the Ministry of Health. Patients are registered for inclusion in this database through the hospital admission authorizations that are issued for patients who are admitted with the condition in question, in accordance with the description under the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10).

The disease codes used for the diagnosis of OA were included in the ICD-10 category M17. The hospitals included in this study are listed in **Appendix 1**. The procedure codes used in the National Hospital Discharge Survey (NHDS) for identifying TKA and RTKA were 04.08.05.006-3 and 04.08.05.005-5, respectively.

Patients who underwent TKA and/or RTKA were assessed. All of these patients were registered in the TABNET software. Partial arthroplasty procedures (unicompartmental and patellofemoral) were excluded.

## Statistical analysis

The prevalence of knee arthroplasty procedures was estimated for each gender, as the number of primary procedures (TKAs) and number of revisions (RTKAs). The variables assessed are presented in tables showing absolute and relative frequencies. The normality of the variables was tested using the Shapiro-Wilk test, and the ratios of the variables were compared using a test for the equality of two proportions.<sup>21</sup> Trend analysis was carried out using polynomial regression models. These models were chosen for their high power, from a statistical perspective, and for the ease with which they can be created and interpreted.<sup>23</sup>

All of the analyses were conducted using a significance level of 5%. The alternatives of two-tailed hypotheses were always taken into consideration.

The information gathered was compiled into a database using Excel for Windows and the statistical analysis was carried out using the STATA 11 SE and Minitab 16 software.

## RESULTS

The total number of knee arthroplasty procedures carried out in the study period in the state of São Paulo was 10,952 (7,891 females and 3,061 males), with an annual average of 1,369 (ranging from 921 to 2,259) and a standard deviation of 481.

The total number of TKA procedures was 9,271, with an annual average of 1,159 (ranging from 830 to 1,839) and a standard deviation of 361. The ratio of TKA procedures to RTKA procedures was 85%, which was statistically significant ( $P < 0.0001$ ), i.e. 5.5 times as many TKA procedures as RTKA ones were carried out (Table 1).

Analysis on the knee arthroplasty data (Table 2) showed that the number of female cases (72%) was significantly greater than the number of male cases. This difference was statistically significant ( $P < 0.0001$ ). This gender bias was maintained with regard to comparing the data relating to TKA. It could be seen that the numbers of TKA procedures on both females and males is rising (both with  $P < 0.001$ ) and that 2.6 times as many procedures are carried out on females. The growth trend for the female population is more pronounced than that of the male population. In 2003, 627 TKA procedures were carried out on females and 203 on males. In 2010, 1,325 TKA procedures were carried out on females and 514 on males. This represents an increase of 133% for women and 153% for men (Figure 1).

**Table 1.** Distribution of primary total knee arthroplasty (TKA) and revision total knee arthroplasty (RTKA) procedures from 2003 to 2010

Type of surgery	n (%)	Average	SD	Median	Min	Max	P
TKA	9,271 (85%)	1,158	361	1,053	830	1,839	< 0.0001
RTKA	1,681 (15%)	210	127	151	91	420	
<b>Total</b>	<b>10,952 (100%)</b>	<b>1,369</b>	<b>481</b>	<b>1,204</b>	<b>921</b>	<b>2,559</b>	

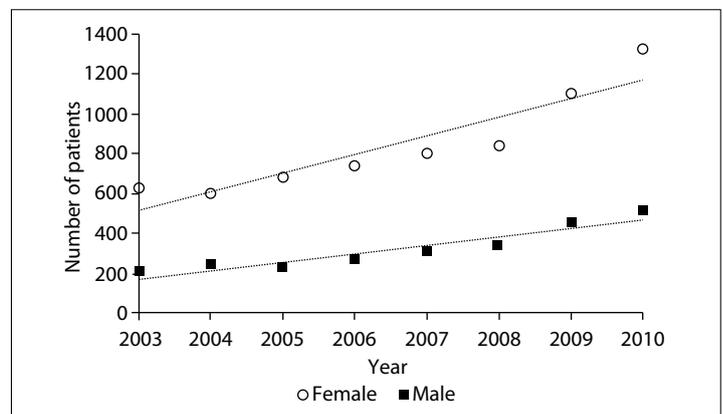
**Table 2.** Distribution of revision total knee arthroplasty (RTKA) and total knee arthroplasty (TKA) procedures according to gender between 2003 and 2010

Type of prosthesis	Gender		Total n (%)	P
	Female n (%)	Male n (%)		
TKA	7,891 (72%)	3,061 (28%)	10,952 (100%)	< 0.0001
RTKA	1,177 (70%)	504 (30%)	1,681 (100%)	< 0.0001

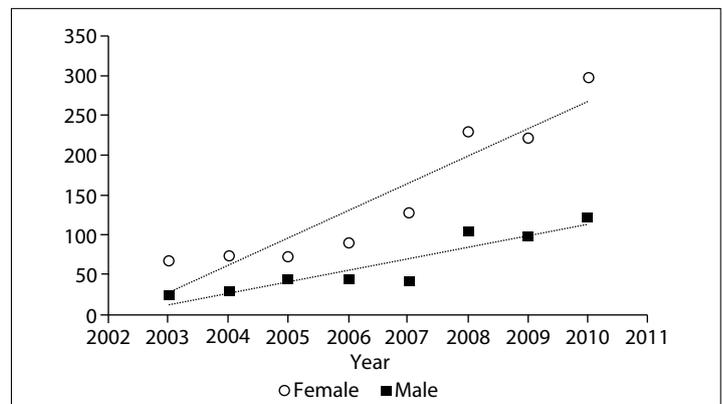
A total of 1,681 RTKA procedures were carried out, with an annual average of 210 (ranging from 91 to 420) and a standard deviation of 127. A significantly greater proportion of the procedures (70%) were conducted on females than on males ( $P < 0.0001$ ) (Table 2).

Figure 2 shows that there was a rising trend in the number of RTKA procedures carried out, for both males and females (both at  $P < 0.001$ ), but that a greater proportion of the procedures were carried out on females, with an average of 2.3 procedures on females for every procedure on a male, which is in keeping with the ratio for TKA. In 2003, there were 67 TKA procedures carried out on women and 24 on men, while in 2010 the numbers were 298 and 122 respectively. This represents growth of 344% for women and 408% for men.

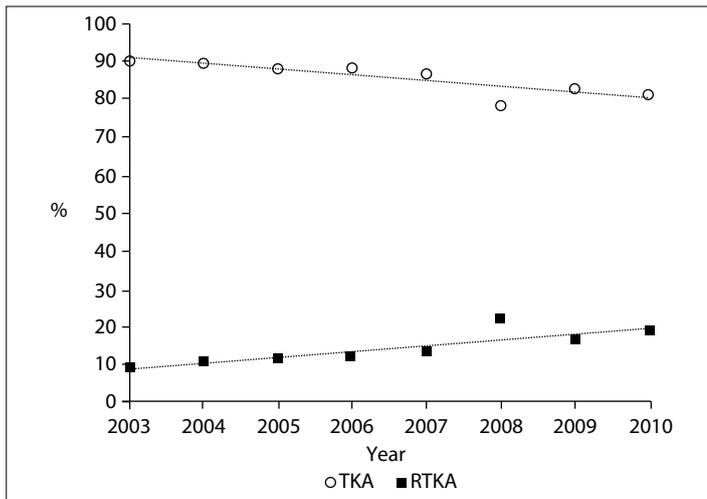
It can be seen that the number of TKA procedures is growing in absolute terms (Table 1). However, the ratio of primary TKA to revision TKA procedures has fallen year on year, as shown in Figure 3. In 2003, there was one revision operation for every nine primary operations, whereas in 2010, this ratio fell to one RTKA for every 4.4 TKA procedures.



**Figure 1.** Trends in primary total knee arthroplasty (TKA) procedures according to gender.



**Figure 2.** Distribution of revision total knee arthroplasties (RTKA) according to gender between 2003 and 2010.



**Figure 3.** Ratio of total knee arthroplasty (TKA) to revision total arthroplasty (RTKA) procedures between 2003 and 2010.

## DISCUSSION

In analyzing the data provided by DATASUS, it can be seen that between 2003 and 2010 there was a change in the epidemiological profile of the knee arthroplasty procedures carried out in the state of São Paulo. There was an increase of 334% in the number of revision TKA procedures carried out on females during the period observed. This increase was significantly greater than in another study in the United States, in which the increase for females was 30%.<sup>24</sup> Our gender-specific analysis on TKA showed that there was an increase of 111% for women, while some similar studies conducted in other countries found proportions of 67%,<sup>24</sup> 74.7%<sup>25</sup> and 90%.<sup>26</sup> This difference may be due to the greater proportion of females in the elderly population and the relatively lower acceptability of TKA among male patients for cultural reasons.

There was an increase in the absolute number of prosthetic knees used. The number of TKA procedures (rise of 122%) more than doubled and the number of RTKA procedures (362%) virtually quadrupled. Other studies, covering similar periods of time, resulted in figures that predicted proportional growth between the two types of surgery, in the United States (140% TKA and 166% RTKA),<sup>24</sup> in Taiwan (99.1% TKA and RTKA 138%)<sup>25</sup> and in Korea (407% TKA and 267% RTKA).<sup>26</sup> A further American survey showed linear progression between TKA and RTKA between 1990 and 2002 (both tripled over that period), with the ratio changing from 10.75 to 10.88.<sup>24</sup> Our series showed a decrease in this relationship between 2003 and 2010, such that the ratio changed from 9.0 to 4.4. This trend differed from the typical ratio of 11 primary TKA procedures for each revision TKA procedure, seen in other studies.<sup>25,26</sup> In our sample, this proportion was not as marked. This may have resulted from the increase in the number of applications for TKA, which has contributed towards raising the RTKA rates.

The most common cause of RTKA is infection.<sup>13,14,15</sup> Preventive measures have been recommended in order to preclude infection after TKA, such as: laminar flow in the operating room, body exhaust suits for the surgical team, waterproof paper drapes, waterproof gowns, double-gloving with outer glove changes after draping and at regular intervals during surgery, skin preparation with 2% chlorhexidine plus 70% alcohol, usage of antibiotic-loaded cements under some circumstances (diabetes, rheumatoid diseases, smokers, previous surgery, malnutrition or coagulopathy), appropriate dosage and choice of systemic prophylactic antibiotics and reduction of allogenic blood transfusion, so as to avoid routine use of surgical drains and bladder catheters, and to minimize the duration of the operation and the number of people circulating during the procedure.<sup>27</sup> These measures have not been adopted routinely in the hospitals analyzed in other countries<sup>16,24,25,26</sup> and this may be a possible reason for the increase in the RTKA rate between 2003 and 2010.

This expansion in both types of arthroplasty can be explained by improvements to instruments and prosthetic implants and improved surgical techniques over recent decades, as well as by the good and sometimes excellent results achieved over the long term among patients who have undergone TKA and RTKA.<sup>9,14,19,28</sup> Another factor that helps explain this progress is the relationship between obesity and knee osteoarthritis,<sup>29,30</sup> in the light of the increasing prevalence of obesity among the populations of Western countries that has been observed over the last decade.<sup>29-32</sup> The present study did not cover this specific variable, nor did it cover other risk factors involved in recommendations for knee arthroplasty surgery in the sample that was evaluated.

This spread of TKA will result in a call for improvements in hospital management and extra training for medical professionals and nursing teams, given that there is a positive association between surgeons' experience and the volume of surgical procedures. Thus, the leading surgical centers that specialize in joint replacements have the highest success rates from knee arthroplasty.<sup>10,31,33</sup> This may have been a factor that contributed towards a higher rate of RTKA. Well-trained knee surgeons who have specialized in TKA and RTKA for one year after their fellowship report fewer complications than do non-specialized surgeons.<sup>34</sup> In the present study, the level of surgeon expertise in knee arthroplasty was not evaluated and may have been a source of poor outcomes from TKA due to technical errors, thereby increasing the RTKA rate.

These numbers are unlikely to be sustained over the long term, given that new materials and more advanced techniques, including those used by surgeons for implanting primary prostheses, will tend to lower the numbers of RTKA procedures.<sup>10,14,35</sup> Nonetheless, in developed countries, the RTKA rate has increased

over time,<sup>24,26</sup> even in situations in which the public healthcare system predominates.<sup>25,36</sup>

The weaknesses of the present study include: the lack of standardization in surgical techniques; the absence of data covering elements such as the sociodemographic variables of age, education level and income, along with patient comorbidities (including obesity), which could help identify risk factors for knee arthroplasty; the absence of the osteoarthritis etiologies and recommendations for the knee arthroplasty procedures performed; and the lack of knowledge relating to materials and implants used for TKA and RTKA. These data were not gathered because of the diversity of information in the medical records and because no interviews with the patients who underwent surgery could be conducted.

## CONCLUSION

The number and prevalence of TKA and RTKA procedures increased in the state of São Paulo during the period between 2003 and 2010. Proportionally, this rise was greater in relation to RTKA than to TKA. This increase was more prominent among female patients.

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### Appendix 1. Hospitals enrolled

Associação Beneficente Nossa Senhora do Pari; Associação Beneficente dos Hospitais Sorocabana; Associação Hospitalar de Bauru; Associação Portuguesa Beneficente de São José do Rio Preto; Casa Nossa Senhora da Paz Ação Social Franciscana; Conjunto Hospitalar de Sorocaba; Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FMRP-USP); Santa Casa de Franca; Hospital Municipal Dr. Waldemar Tebaldi; Hospital de Base de São José do Rio Preto; Hospital das Clínicas da Faculdade de Medicina de Marília (Famema); Hospital Beneficente Unimar; Hospital Emílio Carlos de Catanduva; Hospital Regional de Presidente Prudente; Hospital das Clínicas da Universidade de Campinas (Unicamp); Hospital das Clínicas da Faculdade de Medicina de Botucatu da Universidade Estadual Paulista (Unesp); Hospital de Caridade São Vicente de Paulo; Hospital Universitário de Taubaté; Hospital das Clínicas da Universidade de São Paulo (USP); Hospital Municipal Dr. Carmino Caricchio; Hospital Municipal Dr. Mario Gatti; Hospital Municipal de Paulínia; Hospital São Paulo; Santa Casa de Araçatuba; Hospital Santa Lucinda; Hospital Santa Marcelina; Hospital Santa Lydia; Santa Casa de Jaú; Hospital Geral de Pirajussara; Hospital Geral de Pedreira; Hospital Sanatorinhos de Carapicuíba; Hospital Sanatorinhos de Itu; Hospital Geral de Vila Penteado; Hospital Estadual de Sumaré; Hospital Guilherme Álvaro; Hospital Ipiranga; Santa Casa de Itu; Sociedade Assistencial Bandeirantes de São Paulo; Santa Casa de Araraquara; Santa Casa de Barretos; Hospital da Pontifícia Universidade Católica (PUC) de Campinas.

# Stages of hyperglycemia and common mental disorders in adults – The Brazilian Study of Adult Health (ELSA-Brasil)

Estágios de hiperglicemia e transtornos mentais comuns em adultos - Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil)

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## KEY WORDS:

Diabetes mellitus.  
Prediabetic state.  
Hemoglobin A, glycosylated.  
Depressive disorder.  
Mental disorders.

## PALAVRAS-CHAVE:

Diabetes mellitus.  
Estado pré-diabético.  
Hemoglobina A glicosilada.  
Transtorno depressivo.  
Transtornos mentais.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Diabetes mellitus and depressive disorders frequently coexist. However, this relationship has been little evaluated across stages of hyperglycemia and for a broad range of common mental disorders (CMDs). The objective here was to investigate the association between CMDs and stages of glycemia.

**DESIGN AND SETTING:** Cross-sectional study conducted among civil servants aged 35-74 years participating in the ELSA-Brasil cohort.

**METHODS:** CMDs were classified using the Clinical Interview Schedule – Revised (CIS-R). Glycemia was classified in stages as normal, intermediate hyperglycemia, newly classified diabetes or previously known diabetes, based on oral glucose tolerance testing, glycated hemoglobin (HbA1c), self-reported diabetes and medication use. Blood glucose control was assessed according to HbA1c.

**RESULTS:** CMDs were most prevalent in individuals with previously known diabetes. After adjustments, associations weakened considerably and remained significant only for those with a CIS-R score  $\geq 12$  (prevalence ratio, PR: 1.15; 95% confidence interval, CI: 1.03-1.29). Intermediate hyperglycemia did not show any association with CMDs. For individuals with previously known diabetes and newly classified diabetes, for every 1% increase in HbA1c, the prevalence of depressive disorders became, respectively, 12% and 23% greater (PR: 1.12; 95% CI: 1.00-1.26; and PR: 1.23; 95% CI: 1.04-1.44).

**CONCLUSION:** Individuals with previously known diabetes had higher CIS-R scores. Among all individuals with diabetes, worse blood glucose control was correlated with depressive disorder. No relationship between intermediate hyperglycemia and CMDs was observed, thus suggesting that causal processes relating to CMDs, if present, must act more proximally to diabetes onset.

## RESUMO

**CONTEXTO E OBJETIVO:** Diabetes *mellitus* e transtornos depressivos frequentemente coexistem. No entanto, essa relação tem sido pouco avaliada nos estágios hiperglicêmicos e em uma amplitude maior de transtornos mentais comuns (TMCs). O objetivo foi investigar a associação entre TMCs e estágios de glicemia.

**TIPO DE ESTUDO E LOCAL:** Estudo transversal realizado com funcionários públicos com idade entre 35-74 anos participantes da coorte ELSA-Brasil.

**MÉTODOS:** TMCs foram classificados usando o instrumento Clinical Interview Schedule – Revised (CIS-R). Para a classificação dos estágios de glicemia, foi utilizado o teste de tolerância a glicose, hemoglobina glicada (HbA1c), relato pessoal de diabetes e uso de medicamentos. A glicemia foi categorizada como: normal, hiperglicemia intermediária, classificação nova de diabetes, e diabetes prévio. Controle glicêmico foi avaliado pela HbA1c.

**RESULTADOS:** TMCs foram mais prevalentes nos pacientes com diabetes prévio. Após ajustes, as associações foram consideravelmente enfraquecidas, permanecendo significativas somente para aqueles com escore do CIS-R  $\geq 12$  (razão de prevalência, RP: 1,15; intervalo de confiança de 95%, IC: 1,03-1,29). Hiperglicemia intermediária não teve associação com CMDs. Para aqueles com diabetes prévio e classificação nova de diabetes, para cada aumento de 1% na HbA1c, a prevalência de transtorno depressivo foi, respectivamente, 12% e 23% maior (RP: 1,12; IC: 1,00-1,26 e RP: 1,23; IC: 1,04-1,44).

**CONCLUSÃO:** Aqueles com diabetes prévio tiveram escore do CIS-R mais elevado. Entre todos com diabetes, o controle glicêmico pior foi relacionado ao transtorno depressivo. Não foi observada relação entre hiperglicemia intermediária e TMCs, sugerindo que a relação causal relacionada aos TMCs, se presente, deve agir de forma mais próxima ao início de diabetes.

## INTRODUCTION

Chronic non-communicable diseases (NCDs) are responsible for two thirds of the total number of deaths worldwide.<sup>1</sup> Four diseases, including diabetes mellitus, account for most of these deaths.<sup>2</sup> The prevalence of diabetes is increasing at epidemic proportions, creating a major challenge to healthcare systems worldwide.<sup>3</sup>

NCDs also generate high disease burden and among these, diabetes and neuropsychiatric disorders, especially depressive and anxiety disorders, have taken on utmost importance.<sup>3,4</sup> Depressive disorders occur more frequently among individuals with diabetes and have in fact been considered to be both the cause and the consequence of diabetes.<sup>5,6</sup> On the one hand, receiving a diagnosis of diabetes and needing to cope with this chronic disease that has high morbidity and complex management could, in itself, lead to development of depressive symptoms.<sup>7</sup> On the other hand, factors relating to depressive symptoms, such as obesity, low physical activity or hypercaloric diet, as well as activation of neuroendocrine and inflammatory pathways relating to depression, could also induce insulin resistance and lead to type 2 diabetes. The findings from two meta-analyses on longitudinal studies support each of these directions: a 37% higher risk (relative risk, RR = 1.37; confidence interval, 95% CI: 1.14-1.63) of developing diabetes was seen among adults with depression than among those without depression;<sup>8</sup> and a 24% higher risk (RR = 1.24; CI 95%: 1.09-1.40) of developing depression among individuals with diabetes than among those without diabetes.<sup>9</sup>

The relationship between depression and milder states of hyperglycemia has been less investigated. Moreover, to our knowledge, glycated hemoglobin, which has been widely used to assess glycemic control among individuals with diabetes<sup>10</sup> and has more recently been introduced as a tool to diagnose diabetes and milder states of hyperglycemia, has not been used to assess this relationship across the full range of hyperglycemia, from normality to diabetes.

The Brazilian Longitudinal Study of Adult Health (Estudo Longitudinal de Saúde do Adulto, ELSA-Brasil) was conducted on a sample of 15,105 adults who were assessed using the Clinical Interview Schedule – Revised (CIS-R). This tool makes it possible to diagnose distinct common mental disorders (CMDs) and provides full accounting of hyperglycemia. Thus, ELSA-Brasil offers an excellent opportunity to carry out these broad evaluations.

## OBJECTIVE

The purpose of this study was to investigate associations between stages of glycemia (normality, intermediate states, a single laboratory-based diagnosis of diabetes and a clinical diagnosis of diabetes) and CMDs among ELSA-Brasil participants. We also

investigated associations between glycated hemoglobin levels and common mental disorders across the various stages of hyperglycemia.

## METHODS

### Design and study sample

ELSA-Brasil was a prospective cohort study designed to identify risk factors for diabetes and cardiovascular disease. The details of the study methodology, including design and eligibility criteria, were described previously.<sup>11,12</sup> The cohort comprised 15,105 civil servants who were 35-74 years old at the baseline (2008-2010) and were sampled from universities or research institutes located in six Brazilian state capitals (São Paulo, Belo Horizonte, Porto Alegre, Salvador, Rio de Janeiro and Vitoria). All active or retired employees of the institutions involved, aged 35-74 years, were eligible for the study. The ethics committee of each institution approved the research protocol, and volunteers gave written consent to participate.

### Analytical sample

Out of the 15,105 participants, we excluded 658 participants for whom values relating to the main outcomes, covariates or variables needed to classify stages of diabetes were missing: 10 lacking information on CIS-R, 20 on glycated hemoglobin, 396 on covariates and 232 on self-reported diabetes, treatment for diabetes (medication or diet) or measurements of fasting or two-hour plasma glucose. Thus, our analytical sample was formed by 14,447 participants.

### Common mental disorders (CMDs)

The CIS-R (Clinical Interview Schedule – Revised) was used to measure occurrences of actual psychiatric morbidity (depression and anxiety symptoms).<sup>13</sup> The complete CIS-R version includes 14 sections covering symptoms of CMDs that are present at a level that causes distress and interference with daily activities.

Each section begins with a number of mandatory filter questions that establish whether a particular symptom was present during the past month. The presence of a positive symptom leads to a more detailed assessment of the specific symptom over the past week (frequency, duration, severity and time since onset), in order to determine a score for each section.<sup>14</sup> The CIS-R psychiatric morbidity can be assessed by adding up all 14 symptoms. A CIS-R score  $\geq 12$  was used to indicate an elevated score.<sup>13,15,16</sup>

Additionally, diagnoses of specific disorders were obtained by applying algorithms based on the ICD-10 diagnostic criteria (World Health Organization)<sup>14</sup> and examining the responses to various sections of the CIS-R. The CIS-R allows five diagnostic categories: generalized anxiety disorder, depressive episode, all phobias (agoraphobia, social phobia and simple phobia), obsessive-compulsive disorder and panic disorder. Also, a diagnosis of

mixed anxiety and depression disorder (MADD) can be made in the presence of CIS-R  $\geq 12$  that does not fulfill the criteria for any of these five ICD-10 diagnostic categories. We grouped these disorders into three major groups: all types and severities of depressive episodes, all anxiety disorders (AD; comprising general anxiety disorder, panic disorder, social anxiety disorder, phobias and obsessive-compulsive disorders) and MADD.

### Stages of hyperglycemia and glucose control

Presence of diabetes mellitus was ascertained by means of self-reporting of diagnosis and medication use, fasting glucose measurement and an oral glucose tolerance test (OGTT). Individuals were classified as presenting previously known diabetes if they answered “yes” to either of the following questions: “Have you previously been told by a physician that you had/have diabetes (sugar in the blood)?” or “Have you used medication for diabetes in the past two weeks?”; or if they reported any changes to their dietary habits due to diabetes. The remaining participants were classified according to laboratory measurements. Participants with fasting glucose  $\geq 126$  mg/dl, two-hour plasma glucose  $\geq 200$  mg/dl or HbA1c  $\geq 7\%$  were classified as presenting new-onset diabetes. Those with impaired fasting glucose (fasting glucose  $\geq 110$  mg/dl and  $< 126$  mg/dl) or impaired glucose tolerance (two-hour plasma glucose  $\geq 140$  mg/dl and  $< 200$  mg/dl) were classified as having intermediate hyperglycemia. Those not meeting the above criteria were classified as having normal glycemia.

The stages of glycemia were classified hierarchically as four distinct groups: previously known diabetes ( $n = 1096$ ), newly classified diabetes based only on laboratory measurements ( $n = 1336$ ), intermediate hyperglycemia ( $n = 4841$ ), and normal glycemia ( $n = 7174$ ).

Glucose control was assessed using glycated hemoglobin (HbA1c), which represents the average blood glucose over the past 90 days. HbA1c was measured by means of high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, California, USA), using a method certified by the National Glycohemoglobin Standardization Program.

### Covariates

Sociodemographic characteristics and behavioral risk factors were obtained through structured questionnaires. Anthropometry was obtained using standardized protocols. The body mass index (BMI) was defined as weight (kg) divided by height squared ( $m^2$ ) and the waist-hip ratio as waist circumference divided by hip circumference.<sup>6,17</sup>

### Statistical analysis

Associations between common mental disorders and hyperglycemic stages were estimated using Poisson regression models

with robust variance, separately for the four dichotomous outcomes: CIS-R score  $\geq 12$ , depressive disorders (DD), anxiety disorder (AD) and mixed anxiety and depression disorder (MADD), using the normal glycemia participants as the reference group.

The same models were used to estimate associations between the abovementioned dichotomous outcomes and glucose control defined by HbA1C, separately for each stage of hyperglycemia, except for normal glycemia.

All the analyses were performed using the Statistical Analysis System (SAS) software, version 9.4, taking the significance level to be 5%.

### RESULTS

**Table 1** describes the study participants, overall and stratified according to glucose status. Women predominated (54.1%), as did Caucasians (52.2%), individuals between 45 and 64 years of age (67.5%), married individuals (66.3%) and individuals who reported only doing limited physical exercise during their leisure time (76.8%). The prevalence of common mental disorders (CIS-R  $\geq 12$ ) was 26.7% (95% CI: 26.0-27.4), such that 4.3% (95% CI: 3.9-4.6) of the participants presented a depressive disorder, 16.1% (95% CI: 15.5-16.7) an anxiety disorder and 12.7% (95% CI: 12.2-13.2) a mixed anxiety and depression disorder.

**Table 2** presents prevalence ratios (PR) for the presence of common mental disorders at different stages of hyperglycemia, with normal glucose as the reference category. In minimally adjusted models, individuals with previously known diabetes had greater prevalence of all common mental disorders. Lesser differences in prevalence were observed for individuals classified as diabetic based only on laboratory values. Regarding depressive and anxiety disorders, the differences were not statistically significant. After adjustments had been made for physical activity and also especially for obesity indices, the associations weakened considerably. The only remaining association was for individuals with previously known diabetes and, among them, only for elevated CIS-R scores (prevalence ratio, PR = 1.15; 95% CI: 1.03-1.29). Intermediate states of hyperglycemia were never associated with common mental disorders, even in the minimally adjusted analyses.

**Table 3** presents the associations with a somewhat different approach. Within each stage of glycemia, the association with mental disorders is expressed in terms of a 1% difference in glycated hemoglobin. Here, greater prevalences were observed primarily for individuals with diabetes that was determined through laboratory abnormalities (previously unknown diabetes), and the associations were strongest for depressive disorders (PR = 1.23; 95% CI: 1.04-1.44, in the best-fit model). Again, no association was found with regard to individuals

**Table 1.** Participants' characteristics: overall and according to stage of glycemia. Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010

Characteristic	Stage of glycemia				
	Total (n = 14447)	Previously known diabetes (n = 1096)	Newly classified diabetes (n = 1336)	Intermediate hyperglycemia (n = 4841)	Normal glucose (n = 7174)
	N (%) or mean (SD)	N (%) or mean (SD)	N (%) or mean (SD)	N (%) or mean (SD)	N (%) or mean (SD)
Age (years)					
≤ 44	3164 (21.9)	63 (5.8)	109 (8.2)	828 (17.1)	2164 (30.2)
45 to 54	5690 (39.4)	317 (28.9)	468 (35.0)	1899 (39.2)	3006 (41.8)
55 to 64	4057 (28.1)	456 (41.6)	520 (38.9)	1499 (31.0)	1582 (22.1)
≥ 65	1536 (10.6)	260 (23.7)	239 (17.9)	615 (12.7)	422 (5.9)
Sex					
Male	6625 (45.9)	598 (54.6)	780 (58.4)	2444 (50.5)	2803 (39.1)
Female	7822 (54.1)	498 (45.4)	556 (41.6)	2397 (49.5)	4371 (60.9)
Race/skin color					
Black	2335 (16.2)	265 (24.2)	264 (19.8)	735 (15.2)	1071 (14.9)
"Parda" (mixed)	4063 (28.2)	314 (28.7)	382 (28.6)	1359 (28.1)	2008 (28.0)
White	7540 (52.2)	455 (41.5)	629 (47.1)	2562 (52.9)	3894 (54.3)
Oriental	356 (2.5)	45 (4.1)	39 (2.9)	132 (2.7)	140 (2.0)
Amerindian	153 (1.1)	17 (1.5)	22 (1.6)	53 (1.1)	61 (0.8)
Smoking					
Never	8213 (56.9)	526 (48.0)	645 (48.3)	2670 (55.2)	4372 (60.9)
Former smoker	4341 (30.1)	440 (40.2)	512 (38.3)	1548 (32.0)	1841 (25.7)
Current smoker	1893 (13.1)	130 (11.8)	179 (13.4)	623 (12.8)	961 (13.4)
Physical activity					
Minimal	11095 (76.8)	856 (78.1)	1084 (81.2)	3761 (77.7)	5394 (75.2)
Moderate	2331 (16.1)	191 (17.4)	205 (15.3)	775 (16.0)	1160 (16.2)
Strenuous	1021 (7.1)	49 (4.5)	47 (3.5)	305 (6.3)	620 (8.6)
HbA1c (%)	5.48 (0.99)	7.27 (1.78)	6.07 (1.26)	5.36 (0.57)	5.18 (0.56)
BMI					
Normal	5312 (36.8)	189 (17.2)	261 (19.5)	1378 (28.5)	3484 (48.6)
Overweight	5834 (40.4)	467 (42.6)	531 (39.8)	2155 (44.5)	2681 (37.4)
Obese	3301 (22.9)	440 (40.2)	544 (40.7)	1308 (27.0)	1009 (14.0)
CIS-R					
CIS-R ≥ 12	3854 (26.7)	331 (30.2)	345 (25.8)	1183 (24.4)	1995 (27.8)
Depressive disorders	614 (4.3)	63 (5.8)	46 (3.4)	202 (4.2)	303 (4.2)
Anxiety disorders	2325 (16.1)	194 (17.7)	204 (15.3)	725 (15.0)	1202 (16.8)
Mixed anxiety-depressive disorder	1835 (12.7)	154 (14.1)	176 (13.2)	567 (11.7)	938 (13.1)

SD = standard deviation; HbA1c = hemoglobin A1c; BMI = body mass index; CIS-R = Clinical Interview Schedule - Revised.

with intermediate hyperglycemia, except for borderline significantly higher CIS-R scores in less adjusted models.

## DISCUSSION

Consistent with previous studies,<sup>9</sup> we found that all of the common mental disorders investigated were more prevalent (27% to 72%) among individuals with previously known diabetes than among individuals with normal glycemia, in minimally adjusted models. Das-Munshi et al., using the same instrument (CIS-R) for classifying mental disorders, found a 50% higher prevalence (odds ratio, OR = 1.5; 95% CI: 1.1-2.2) of common mental disorders and a 70% higher prevalence (OR = 1.7; 95% CI: 1.1-2.6) of mixed anxiety and

depression disorders among individuals with previously known diabetes, in similarly minimally adjusted models.<sup>17</sup> We also found that among individuals with previously known diabetes, having a higher level of glycated hemoglobin was associated with a slightly, though statistically significantly greater presence of depressive disorders (12% for every 1% increase in HbA1c), which is consistent with previous reports.<sup>18</sup>

More frequent presence of mental disorders among individuals with diabetes may be explained by the higher burden resulting from having to deal with a chronic disease that presents multiple acute and chronic complications and for which the treatment is long-term and complex. Additionally, two acute complications, hypoglycemia

**Table 2.** Association of common mental disorders with stage of glycemia. Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010

Stage of glycemia	Common mental disorders			
	CIS-R $\geq$ 12	Depressive disorders	Anxiety disorders	Mixed anxiety- depressive disorder
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Previously known diabetes (n = 1096) <sup>a</sup>				
Model 1	1.33 (1.20;1.47)	1.72 (1.30;2.27)	1.27 (1.10;1.47)	1.27 (1.08;1.51)
Model 2	1.30 (1.18;1.44)	1.67 (1.26;2.21)	1.26 (1.08;1.46)	1.25 (1.06;1.48)
Model 3	1.15 (1.03;1.29)	1.31 (0.97;1.78)	1.11 (0.95;1.30)	1.18 (0.98;1.41)
Newly classified diabetes (n = 1336) <sup>a</sup>				
Model 1	1.13 (1.02;1.25)	1.06 (0.77;1.46)	1.10 (0.95;1.27)	1.20 (1.03;1.40)
Model 2	1.10 (1.00;1.21)	1.01 (0.74;1.39)	1.07 (0.93;1.24)	1.17 (1.00;1.36)
Model 3	0.98 (0.88;1.08)	0.79 (0.57;1.09)	0.97 (0.83;1.12)	1.06 (0.90;1.25)
Intermediate hyperglycemia (n = 4841) <sup>a</sup>				
Model 1	0.99 (0.93;1.06)	1.15 (0.96;1.38)	1.00 (0.91;1.08)	1.01 (0.92;1.12)
Model 2	0.98 (0.92;1.05)	1.13 (0.94;1.35)	0.99 (0.90;1.07)	1.00 (0.91;1.11)
Model 3	0.91 (0.86;0.97)	1.02 (0.84;1.23)	0.92 (0.84;1.00)	0.95 (0.86;1.05)

PR = prevalence ratio estimated through Poisson regression with robust variance; <sup>a</sup>normal glycemia participants (N = 7174) are the reference group.

Model 1: adjusted for sex, age, race, marital status and smoking; Model 2: adjusted additionally for physical activity; Model 3: adjusted additionally for body mass index and waist-hip ratio.

**Table 3.** Association<sup>a</sup> between glyated hemoglobin and presence of common mental disorders at different stages of glycemia. Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010

Stage of glycemia	Common mental disorders			
	CIS-R $\geq$ 12	Depressive disorder	Anxiety disorder	Mixed anxiety- depressive disorder
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Previously known diabetes (n = 1096)				
Model 1	0.98 (0.93;1.03)	1.13 (1.00;1.27)	0.98 (0.91;1.05)	0.98 (0.90;1.07)
Model 2	0.98 (0.93;1.03)	1.12 (1.00;1.27)	0.98 (0.91;1.05)	0.98 (0.90;1.07)
Model 3	0.98 (0.93;1.03)	1.12 (1.00;1.26)	0.98 (0.91;1.05)	0.98 (0.90;1.07)
Newly classified diabetes (n = 1336)				
Model 1	1.06 (1.00;1.13)	1.25 (1.05;1.47)	1.10 (1.01;1.19)	1.03 (0.93;1.15)
Model 2	1.06 (1.00;1.13)	1.25 (1.06;1.47)	1.10 (1.01;1.19)	1.03 (0.93;1.15)
Model 3	1.06 (1.00;1.13)	1.23 (1.04;1.44)	1.09 (1.00;1.18)	1.02 (0.91;1.15)
Intermediate hyperglycemia (n = 4841)				
Model 1	1.09 (1.00;1.18)	1.04 (0.80;1.33)	1.03 (0.91;1.16)	1.07 (0.94;1.23)
Model 2	1.08 (1.00;1.18)	1.03 (0.80;1.32)	1.03 (0.91;1.16)	1.07 (0.93;1.23)
Model 3	1.05 (0.96;1.14)	1.00 (0.78;1.29)	1.00 (0.88;1.12)	1.04 (0.91;1.20)

PR = prevalence ratio estimated through Poisson regression with robust variance; <sup>a</sup>expressed for a 1% difference in glyated hemoglobin.

Model 1: adjusted for sex, age, race, marital status and smoking; Model 2: adjusted additionally for physical activity; Model 3: adjusted additionally for body mass index and waist-hip ratio.

and hyperglycemia, may activate the hypothalamic/pituitary/adrenal axis and thus lead to depression.<sup>19</sup> Altered neurotrophins, presence of inflammatory mediators and reduced white mass are also related to depression among individuals with diabetes.<sup>20</sup>

Interestingly, among individuals who did not know that their glucose levels had reached the criterion for defining diabetes, we found a 23% greater prevalence (PR = 1.23; 95% CI: 1.04-1.44) of depressive disorders with a 1% increase in glyated hemoglobin. This somewhat larger association is unlikely to result from the burden of treating diabetes and its complications, since the affected individuals were unaware of their high glucose status and were also more likely to be in earlier stages of the disease and, as such, less likely to suffer from its complications. However, it is possible that

symptomatic hyperglycemia was present in some of them, and this may have been causing depressive symptoms through activation of the hypothalamic/pituitary/adrenal axis, or through production of symptoms such as fatigue and insomnia, which are among the criteria used for determining the presence of depression.

Another possible explanation for the associations found is that hyperglycemia results, in part, from a complex inflammatory/metabolic condition that may also produce psychoneuroendocrine comorbidity.<sup>21,22</sup> In fact, as has been demonstrated with various inflammation markers,<sup>23-27</sup> mild chronic inflammation precedes and predicts the development of diabetes in adults.

On the other hand, having a depressive disorder has been shown to predict poorer glycemic control among individuals

with type 2 diabetes.<sup>28</sup> However, the fact that in our analyses, intermediate hyperglycemia was never associated with common mental disorders argues somewhat against this directionality. Additionally, we did not find any association between glycated hemoglobin and common mental disorders among individuals with intermediate hyperglycemia.

Given the possible bidirectionality of the associations between diabetes and common mental disorders, caution must be maintained in interpreting causality. Golden et al.<sup>5</sup> examined both directions of this association and found that there was a modest association between baseline depressive symptoms and the incidence of type 2 diabetes that was partially explained by lifestyle factors. They also found that individuals with type 2 diabetes that was under treatment more frequently developed depressive symptoms, and that this association was not substantively affected by adjustment for potential confounding or mediating factors.

Our study has some notable strengths. To our knowledge, it is the most comprehensive cross-sectional study to date, given that we investigated both a large spectrum of hyperglycemic stages and several common mental disorders. We undertook a full assessment of diabetes, encompassing participants' reports on diagnoses and medication use, an oral glucose tolerance test and measurements on glycated hemoglobin. We also carefully assessed common mental disorders. Our relatively large sample size enabled adjustment for several potential confounding factors, thus demonstrating associations independent of smoking, marital status, age, sex, race and, to some extent, sedentary behavior and obesity.

Some limitations of our study need to be borne in mind. First, the cross-sectional nature of our findings limits interpretation of the possible direction of the associations presented. Second, we were unable to distinguish types of diabetes, although it is likely that the vast majority of the subjects had type 2 diabetes. Third, our determination of the presence of mental disorders did not evaluate their recurrence or chronicity.<sup>17</sup> Fourth, we did not consider the role of antidiabetic or antidepressive medication in the associations. It is possible, for instance, that metformin use might decrease the risk of depression, which could explain the slightly lower prevalence ratio for depression seen among treated cases than among the newly diagnosed cases.<sup>20,29,30</sup> Finally, modeling these associations is tricky, given their probable bidirectionality, their multiple common causes and the possibility that various covariates may act as confounders and mediators. In fact, we found that after adjustments for lower physical activity levels and greater obesity indices, both of which may be a cause or a consequence of diabetes or its treatment, the associations between common mental disorders and known diabetes weakened considerably, and remained statistically significant only for individuals who presented an elevated CIS-R score (PR = 1.15; 95% CI: 1.03-1.29).

Our findings strengthen the previous results in the literature, through documenting the coexistence of diabetes and common

mental disorders, especially depression. Adequate glucose control, in addition to preventing diabetic complications, may also prevent depressive disorders. If so, additional investigations will be required in order to determine whether this prevention results from glucose control *per se* or whether it arises from the ability to cope with the disease, for instance in terms of self-efficacy in managing diabetes and other conditions such as weight control and physical activity.<sup>2</sup>

## CONCLUSION

Individuals with previously known diabetes had higher CIS-R scores. Among all individuals with diabetes, worse blood glucose control was correlated with depressive disorder. No relationship between intermediate hyperglycemia and CMDs was observed, thus suggesting that causal processes relating to CMDs, if present, must act more proximally to diabetes onset.

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# The effect of sleep apnea severity on cardiac autonomic activity during night time in obstructive sleep apnea patients

O efeito da gravidade da apneia do sono sobre atividade cardíaca autonômica durante o período noturno em pacientes com apneia obstrutiva do sono

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## KEY WORDS:

Heart rate.  
Arrhythmias, cardiac.  
Death, sudden, cardiac.  
Sleep apnea syndromes.  
Sleep apnea, obstructive.

## PALAVRAS-CHAVE:

Frequência cardíaca.  
Arritmias, cardíacas.  
Morte súbita cardíaca.  
Síndromes da apneia do sono.  
Apneia do sono tipo obstrutiva.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Impaired autonomic cardiac function is an important consequence of obstructive sleep apnea (OSA). This impairment is mainly due to intermittent hypoxia episodes following apneas. However, the impact of apnea severity on autonomic cardiac function remains unclear. The aim of this study was to evaluate the relationship between the severity of sleep apnea and heart rate turbulence (HRT) and heart rate variability (HRV) in OSA.

**DESIGN AND SETTING:** Observational cross-sectional study conducted in the Departments of Cardiology and Pulmonary Diseases, Afyon Kocatepe University, Turkey.

**METHODS:** 106 patients with OSA and 27 healthy volunteers were enrolled. Based on apnea hypopnea index (AHI) values, obstructive sleep apnea severity was classified as follows: mild OSA (AHI  $\geq 5$  and  $< 15$ ), moderate OSA (AHI  $\geq 15$  and  $\leq 30$ ) and severe OSA (AHI  $> 30$ ). HRV and HRT parameters were assessed via 24-hour digital Holter electrocardiogram recordings for all subjects.

**RESULTS:** HRV and HRT results were significantly lower among OSA patients than among control subjects ( $P < 0.05$ ). However, there were no significant differences in HRT and HRV between the three patient subgroups. Correlations did emerge between AHI and the NN-interval parameter RMSSD and between oxygen desaturation and turbulence slope (respectively:  $r = -0.22$ ,  $P = 0.037$ ; and  $r = -0.28$ ,  $P = 0.025$ ).

**CONCLUSION:** HRT and HRV results deteriorate in OSA. Correlations between apnea severity and these parameters seem to be present.

## RESUMO

**CONTEXTO E OBJETIVO:** Função autonômica cardíaca prejudicada é consequência importante da apneia obstrutiva do sono (AOS). Este prejuízo deve-se principalmente a episódios de hipóxia intermitente após apneias. No entanto, o impacto da gravidade da apneia na função cardíaca autonômica permanece obscuro. O objetivo deste estudo foi avaliar a relação entre gravidade da apneia do sono com turbulência da frequência cardíaca (TFC) e variabilidade da frequência cardíaca (VFC) em pacientes com AOS.

**DESENHO E LOCAL:** Estudo observacional transversal conduzido nos Departamentos de Cardiologia e Doenças Pulmonares, Afyon Kocatepe University, Turkey.

**MÉTODOS:** 106 pacientes com AOS e 27 voluntários saudáveis foram recrutados. Com base nos valores do índice de apneia-hipopneia (IAH), a gravidade da apneia obstrutiva do sono foi classificada assim: AOS leve (IAH  $\geq 5$  e  $< 15$ ), AOS moderada (IAH  $\geq 15$  e  $\leq 30$ ) e AOS grave (IAH  $> 30$ ). Parâmetros da VFC e TFC foram avaliados por meio de gravações de eletrocardiograma digital Holter de 24 horas para todos os sujeitos.

**RESULTADOS:** Os resultados da VFC e TFC foram significativamente menores nos pacientes com OSA, em comparação com indivíduos controle ( $P < 0,05$ ). No entanto, não houve diferenças significativas em VFC e TFC, entre os três subgrupos de pacientes. Correlações surgiram entre IAH e o parâmetro do intervalo-NN, RMSSD, e entre dessaturação de oxigênio e declive da turbulência (respectivamente;  $r = -0,22$ ,  $P = 0,037$ ; e  $r = -0,28$ ,  $P = 0,025$ ).

**CONCLUSÃO:** Os resultados da VFC e TFC deterioraram em AOS. Parece haver relação entre a gravidade da apneia e tais parâmetros.

## INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent total apnea or partial hypopnea due to narrowed upper airways during sleep.<sup>1</sup> The current estimates for the prevalence of moderate-to-severe sleep-disordered breathing (apnea-hypopnea index, AHI, measured as events/hour,  $\geq 15$ ) are 10% among 30-49 year-old men; 17% among 50-70 year-old men; 3% among 30-49 year-old women; and 9% among 50-70 year-old women, according to the study by Peppard et al.<sup>2</sup> The prevalence of obstructive sleep apnea syndrome among Brazilian railroad workers has been found to be 35%.<sup>3</sup>

OSA is associated with cardiovascular diseases, including cardiac arrhythmias,<sup>4</sup> myocardial infarction,<sup>5</sup> chronic heart failure<sup>6</sup> and pulmonary hypertension.<sup>7</sup> The mechanism underlying cardiovascular diseases is complex and not fully understood in relation to OSA. Arrhythmias are considered to arise from changes in the cardiac autonomic balance due to hypoxia during apnea.<sup>8</sup>

There is a significant correlation between autonomic dysfunction and cardiovascular mortality.<sup>9</sup> Baroreceptor reflex sensitivity, heart rate turbulence (HRT) and heart rate variability (HRV) are parameters reflecting cardiac autonomic functions. HRV and baroreceptor reflex sensitivity are believed to evaluate different aspects of autonomic control. While a moderate relationship has been determined between HRV and baroreceptor reflex sensitivity, there is a strong relationship between HRT and baroreceptor reflex sensitivity. Therefore, it has been suggested that HRT should be used as an evaluation parameter instead of baroreceptor reflex sensitivity.<sup>10,11</sup>

HRV<sup>12,13</sup> and HRT<sup>14</sup> provide important information regarding autonomic cardiac function. HRV measures the oscillation in successive cardiac cycles as well as the oscillations between instantaneous heart rates.<sup>13</sup> Previous studies have determined that a reduction in HRV is predictive of increased cardiac mortality.<sup>15</sup> HRT is defined as the sinus rhythm cycle-length fluctuation after isolated premature ventricular beats.<sup>16</sup> HRT evaluation has been deemed appropriate for risk estimation after acute myocardial infarction<sup>17</sup> and as a prognostic evaluator for heart failure<sup>18</sup> and other pathological conditions.<sup>16</sup>

Autonomic cardiac functions in OSA patients have been the focus of attention for researchers. Previous studies revealed deteriorations in HRT and a relationship between HRT and the severity of the apnea.<sup>19-21</sup> However, the results relating to HRV in these patients have been divergent; reductions and no changes in HRV have been reported in different studies.<sup>20-22</sup>

## OBJECTIVE

Therefore, the aims of the present study were to investigate whether both HRT and HRV parameters are impaired in patients

with OSA and to make correlations between these parameters and disease severity.

## METHODS

### Study design, ethics and setting

This study was designed as an observational cross-sectional study with a convenience sample. Interim power analyses were performed and detected a 90% statistical power.

The study was conducted in our Departments of Cardiology and Pulmonary Diseases between March 1, 2014, and November 1, 2014. The Ethics Committee of the Afyon Kocatepe University School of Medicine approved this study. All patients and control subjects gave their informed consent prior to inclusion.

### Participants

The study sample included subjects consulted at a sleep laboratory for clinically suspected OSA. These were all the consecutive patients examined over an eight-month period between March 2014 and November 2014. After polysomnographic examination, subjects with five or more obstructive apnea, mixed apnea or hypopnea events per hour were diagnosed as having OSA in accordance with the criteria of the American Academy of Sleep Medicine. Subjects presenting simple snoring, with apnea-hypopnea index less than 5 and no systemic diseases were enrolled in the control group. Subjects with diabetes mellitus, hypertension, ischemic heart disease, heart failure, renal disease, chronic inflammatory diseases, disorders of the autonomic nervous system or endocrine system, histories of drug use affecting the autonomic nervous system, pulmonary diseases or a smoking habit were excluded from the study.

Systolic and diastolic blood pressure of all patients and controls were measured from the right arm using a mercury manometer, after they had rested in a seated position for at least five minutes. Blood pressure was measured using a mechanical sphygmomanometer before polysomnographic evaluation. Patients whose office systolic blood pressure was  $\geq 140$  mmHg and/or diastolic blood pressure was  $\geq 90$  mmHg were considered to present arterial hypertension. Body weight and height were also assessed. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ).

### HRT and HRV analysis

Full-night Holter monitoring (Reynolds Medical, Pathfinder Software version V8.255) was performed on all subjects. HRT parameters, turbulence onset (TO) and turbulence slope (TS) were calculated using the HRT View software version 0.60-0.1 (downloadable via [www.h-r-t.com](http://www.h-r-t.com)). All Holter recordings were checked, and any visually observed artifacts that the program accepted as normal premature ventricular beats were excluded from

the analyses. TO reflects the initial heart rate acceleration after a premature ventricular beat, whereas TS represents the subsequent heart rate deceleration following a premature ventricular beat. TO was determined as the difference between the mean of the two RR intervals after premature ventricular beats and the mean of the two RR intervals before premature ventricular beats divided by the mean value of two RR intervals before premature ventricular beats. TS was defined as the maximum positive value of the slope of a regression line computed over any sequence of five subsequent sinus RR intervals within the first 15 sinus intervals after premature ventricular beats. TO values determined for all suitable premature ventricular beats were averaged to obtain a final TO value. TO < 0% and TS > 2.5 ms/RR are considered to be normal values.<sup>22</sup>

The HRV parameters used in the present study were selected in accordance with guidelines from the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.<sup>13</sup> The following time domain HRV parameters were computed: standard deviation of all normal-to-normal (NN) intervals (SDNN), standard deviation of NN interval averages during all five-minute segments across all recordings (SDANN), mean of the standard deviation of all NN intervals for all five-minute segments across all recordings (SDNN index), integral of the density distribution of NN intervals divided by the maximum of the density distribution (HRV triangular index) and root mean square of the sum of squares for differences between adjacent NN intervals (RMSSD).

### Polysomnography

Full-night polysomnography (PSG) was recorded for all subjects using a digital PSG system (E series, Compumedics, Abbotsford, Victoria 3067, Australia) within the Department of Chest Diseases, Afyon Kocatepe University. Respiratory and physical changes were recorded during sleep. For all patients, electroencephalography, electrooculogram and submental electromyography data were obtained. Oronasal airflow was measured using a nasal cannula placed in the nose. Thoracoabdominal movements were evaluated by means of sensors placed on the chest and abdomen to determine respiratory patterns. A pulse oximeter and electrocardiography electrodes were used to measure oxygen saturation and heart rate, respectively. Leg movements were examined using electromyography sensors positioned on the anterior tibialis muscle. Sleep stages were scored in accordance with standard criteria from the American Academia of Sleep Medicine.<sup>23</sup>

Apnea is defined as a drop in the peak signal excursion by  $\geq 90\%$  of the pre-event baseline for at least 10 seconds. Hypopnea is an event in which there is a  $\geq 30\%$  reduction in nasal pressure signal excursions from baseline and an associated  $\geq 4\%$  desaturation from the pre-event baseline for at least 10 seconds. Obstructive events were defined as ongoing thoracoabdominal

effort in cases of partial or complete airflow cessation. The apnea-hypopnea index (AHI) was the number of apnea or hypopnea events recorded during the study per hour of sleep. The severity of OSA was defined as mild (AHI  $\geq 5$  and  $< 15$ ), moderate (AHI  $\geq 15$  and  $\leq 30$ ) or severe (AHI  $> 30$ ). The oxygen desaturation index (ODI) was also calculated, as the total number of oxygen desaturation events divided by total duration of sleep.

All polysomnographic data was interpreted by a sleep specialist who was blind to the subjects' HRT and HRV analysis results.

### Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Co., Armonk, NY, USA). Data were expressed as the mean  $\pm$  SD, medians (with interquartile range), or number (and %). Assumptions of normal distribution were tested using the Kolmogorov-Smirnov test. Categorical variables between groups were compared using a chi-square test. Differences between the patient group and control subjects were tested using Student's t test for parametric variables and the Mann-Whitney U test for nonparametric variables. Comparisons between more than two groups (patients with mild, moderate or severe OSA and control subjects) in relation to variables with homogenous distributions were also analyzed using one-way analysis of variance (ANOVA) and Tukey's test for post-hoc analyses. Comparisons between more than two groups in which the variables were not normally distributed were made using the Kruskal-Wallis test. In addition, analysis of covariance (ANCOVA) was performed to compare HRT and HRV parameters among the groups, controlling for BMI. Correlations between AHI, TO with AHI, and total oxygen desaturation were analyzed using Spearman's rho correlation coefficients. An alpha level of  $P < 0.05$  was accepted as significant.

## RESULTS

### Demographic characteristics

The study subjects consisted of 106 newly diagnosed patients with OSA (mean age  $49.2 \pm 11.2$  years) and 27 healthy controls (mean age  $47.2 \pm 7.9$  years). The patients included 30 with mild OSA (mean age  $49.1 \pm 10.4$  years), 34 with moderate OSA (mean age  $51.2 \pm 6.8$  years) and 42 with severe OSA (mean age  $54.4 \pm 8.3$  years) OSA. There were no differences between the groups in terms of age or gender. However, there was a significant difference between the groups in terms of BMI. The subjects' demographics are depicted in **Table 1** and **Table 2**.

### HRV and HRT parameters

HRT measurements were obtained from 84 individuals ( $n = 24$  controls,  $n = 21$  with mild OSA,  $n = 20$  with moderate OSA and  $n = 19$  with severe OSA). For the remaining subjects, HRT could

**Table 1.** Demographics, polysomnographic results and HRV and HRT parameters among control subjects and patients with OSA

	Subjects without OSA n = 27	Patients with OSA n = 106	P-value
Age (years)	47.2 ± 7.9	49.2 ± 11.2	0.1*
Gender (F/M)	11/16	40/66	0.84†
BMI (kg/m <sup>2</sup> )	27.7 ± 5.6	33.7 ± 6.3	<b>0.001</b> ‡
AHI	1.75 ± 1.5	30 ± 23.5	< <b>0.001</b> ‡
Total duration of sleep	394 (304-396)	325 (188-519)	0.06*
Sleep efficacy	86.5 ± 6.8	77.9 ± 11.1	0.125‡
Total oxygen desaturation	3 (2-13)	101 (34-622)	< <b>0.001</b> *
ODI	2.2 (0.3-3.2)	27.1 (3.2-96.8)	< <b>0.001</b> *
TO (%)	-3.19 ± 1.6	-2.2 ± 1.4	<b>0.004</b> ‡
TS (ms/RR)	8.3 (3.8-8.6)	6.2 (2-17.3)	0.89*
SDNN (ms)	143 ± 37	90 ± 25	< <b>0.001</b> ‡
SDNNI (ms)	63 ± 27	45 ± 13	< <b>0.001</b> ‡
SDANN (ms)	116 (88-157)	74 (29-142)	< <b>0.001</b> *
RMSSD (ms)	42 ± 36	25 ± 10	<b>0.003</b> ‡
TI (ms)	25 (23-41)	22 (8-50)	< <b>0.001</b> *
SBP (mmHg)	108.7 ± 33.2	123.1 ± 10.8	<b>0.049</b> ‡
DBP (mmHg)	72.2 ± 14.6	73 ± 8.1	0.51‡
Mean HR (bpm)	70 (59-71)	74 (56-97)	0.14*

Data were shown as mean ± SD or median (with interquartile range). Categorical variables are defined as percentages.

\*Mann-Whitney U test; †chi-square test; ‡Student's t test.

OSA = obstructive sleep apnea; F = female; M = male; BMI = body mass index; AHI = apnea-hypopnea index; ODI = oxygen desaturation index; TO = turbulence onset; TS = turbulence slope; SDNN = standard deviations of all (normal-to-normal) NN intervals; SDNNI = mean of the standard deviation of all NN intervals for all 5-min segments of the entire recording; SDANN = standard deviation of averages of NN intervals in all 5-min segments of the entire recording; TI = triangular index; RMSSD = the square root of the mean of the sum of the squares of differences between adjacent NN intervals; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BPM = beats per minute.

**Table 2.** Polysomnographic results and HRT and HRV parameters compared between subgroups

Parameters	Subjects without OSA n = 27	Patients with mild OSA n = 30	Patients with moderate OSA n = 34	Patients with severe OSA n = 42	P-value
Age (years)	47.2 ± 7.9	49.1 ± 10.4	51.2 ± 6.8	54.4 ± 8.3	0.1
Gender (F/M)	11/16	17/13	9/25	14/28	0.07
BMI (kg/m <sup>2</sup> )	27.7 ± 5.7	31.8 ± 6.1*	32.4 ± 5.3*	37.1 ± 6.4*	<b>0.002</b>
AHI	1.75 ± 1.5	10.7 ± 2.6	21.7 ± 3.6	58.7 ± 19	< <b>0.001</b>
Total duration of sleep	372 ± 45.3	322 ± 26.9	338.2 ± 77.7	305 ± 69.3	0.249
Sleep efficacy	88 (78-92)	81 (67-92)	80 (61-98)	75 (52-97)	0.269
Total oxygen desaturation	5.2 ± 5.2	92 ± 90	130 ± 72.5	330 ± 132	< <b>0.001</b>
ODI	2.2 (0.3-3.2)	11.8 (7-67.7)	24.8 (6.4-51)	56.6 (3.2-97)	< <b>0.001</b>
TO (%)	-3.19 ± 1.6	-2.06 ± 1.2*	-2.06 ± 0.8*	-1.9 ± 1.2*	<b>0.005</b>
TS (ms/RR)	8.3 (3.8-8.6)	5.5 (3.2-17.2)	8.3 (2.2-14)	6.4 (2-13.8)	0.98
SDNN (ms)	143 ± 37	96 ± 29*	95 ± 2*	79 ± 20*	< <b>0.001</b>
SDNNI (ms)	63 ± 27	45 ± 13*	47 ± 13*	42 ± 14*	< <b>0.001</b>
SDANN (ms)	116 (88-157)	69 (29-142)*	77 (58-132)*	73 (38-140)*	< <b>0.001</b>
RMSSD (ms)	30 (20-81)	23 (10-56)*	23 (10-37)*	33 (8-60)	<b>0.007</b>
TI (ms)	25 (23-41)	20 (8-44)*	21.5 (13-50)*	22 (10-42)*	< <b>0.001</b>
SBP (mmHg)	108.7 ± 33.2	121.6 ± 11.9*	120 ± 7.7*	119 ± 6*	<b>0.03</b>
DBP (mmHg)	72.2 ± 14.6	69.7 ± 7.3	74.7 ± 8.9	75.1 ± 7.4	0.1
Mean HR (bpm)	66 ± 10	74 ± 9	71 ± 10	75 ± 11	0.10

Data are shown as mean ± SD or median (with interquartile range). Categorical variables are defined as percentages.

Comparisons between patients with mild, moderate or severe OSA and control subjects were analyzed using the Kruskal-Wallis test or ANOVA and Tukey's test for post-hoc analyses and significant p values were presented bold

\*P < 0.05: between subjects without OSA and patients with mild, moderate and severe OSA

OSA = obstructive sleep apnea; F = female; M = male; BMI: body mass index; AHI = apnea-hypopnea index, ODI = oxygen desaturation index, TO = turbulence onset; TS = turbulence slope; SDNN = standard deviations of all normal-to-normal (NN) intervals; SDNNI = mean of the standard deviation of all NN intervals for all 5-min segments of the entire recording; SDANN = standard deviation of averages of NN intervals in all 5-min segments of the entire recording; TI = triangular index; RMSSD = the square root of the mean of the sum of the squares of differences between adjacent NN intervals; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BPM = beats per minute.

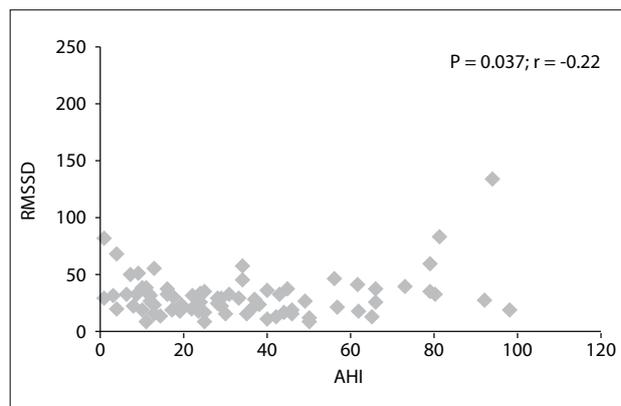
not be calculated due to a lack of ventricular premature beats during Holter recording.

No significant differences were found between OSA patients and control subjects in terms of total sleep time, sleep efficacy, age, TS, blood pressure, and heart rate. The TO, SDNN, SDNNI, SDANN, RMSSD, and TI values were significantly lower among OSA patients than among control subjects (Table 1). ANCOVA was performed to compare HRT and HRV parameters between the groups, controlling for BMI. However, significant differences between groups continued after eliminating the influence of BMI.

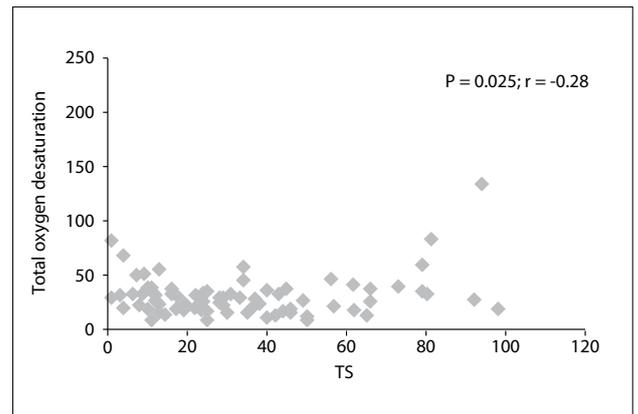
The subjects were divided into four groups according to their AHI values. The subjects without OSA ( $n = 27$ ) ( $AHI < 5$ ), patients with mild OSA ( $AHI 5-15$ ) ( $n = 30$ ), patients with moderate OSA ( $n = 34$ ) and patients with severe OSA ( $AHI > 30$ ) ( $n = 42$ ) were compared with regard to HRV, HRT and polysomnographic parameters (Table 2). Post-hoc analyses were performed. No significant differences between mild OSA patients, moderate OSA patients and severe OSA patients in terms of HRT and HRV parameters emerged. However, there were significant differences between mild OSA patients and control subjects, between moderate OSA patients and control subjects and between severe OSA patients and control subjects in terms of TO, SDNN, SDNNI, SDANN, RMSSD and TI values (Table 2).

When the correlation between AHI (which reflects disease severity) and TO was investigated, no statistically significant correlation was observed ( $P = 0.356$ ;  $r = -0.11$ ). There was no statistically significant correlation between total oxygen desaturation and TO ( $P = 0.631$ ;  $r = -0.06$ ). There was also no statistically significant correlation between total oxygen desaturation and TO ( $P = 0.631$ ;  $r = -0.06$ ). However, RMSSD and AHI were negatively correlated ( $P = 0.037$ ;  $r = -0.22$ ; Figure 1).

A significant correlation between total oxygen desaturation and TS ( $P = 0.025$ ;  $r = -0.28$ ) was observed (Figure 2). In addition, there were negative correlations between ODI and SDNN, SDANN



**Figure 1.** Relationship between apnea hypopnea index (AHI) and root mean square of the successive differences (RMSSD).



**Figure 2.** Relationship between total oxygen desaturation and turbulence slope (TS).

and TI (respectively:  $P = 0.002$ ,  $r = -0.28$ ;  $P < 0.001$ ,  $r = -0.34$ ; and  $P = 0.01$ ,  $r = -0.23$ ).

## DISCUSSION

The findings from the present study revealed that the patients with OSA had lower values for HRV and HRT than those of the control subjects. Such reductions were observed even in patients with mild OSA. Although there was no significant difference between patient groups in terms of HRV and HRT parameters, significant correlations between TS and total oxygen desaturation, between RMSSD and AHI, and between ODI and SDNN, SDANN and TI were found.

Previous studies revealed that HRV and HRT worsen in OSA.<sup>19-21,24-27</sup> The authors of these studies thought that this deterioration might be due to hypoxia during periods of apnea. Ari et al.<sup>19</sup> reported that HRT worsened in OSA while HRV did not change and there was a relationship between HRT and AHI. Aytemir et al.<sup>20</sup> observed increased myocardial vulnerability and autonomic nervous system imbalance in OSA cases. They found that HRT, HRV and QT dynamicity parameters were significantly worse among patients with OSA. Furthermore, a correlation was revealed between AHI and HRT. However, they did not find any relationship between AHI and HRV. These authors<sup>20</sup> also showed the presence of autonomic balance changes in favor of the sympathetic nervous system at night and hypoxemia relating to apnea. Erdem et al.<sup>25</sup> investigated HRT parameters among patients with pure OSA. They found that the OSA group had a significantly higher mean TO than the control group, and that the AHI of the OSA group was positively correlated with TO. Our study supports the findings of previous studies. TO was significantly higher in patients with OSA than in the control group and, although there were no correlations between AHI and HRT parameters, there was a correlation between total oxygen desaturation and TS in our study.

Yang et al.<sup>21</sup> also showed that HRV did not change while HRT worsened during sleep among patients with OSA, and that alterations in nighttime HRT correlated with sleep-disordered breathing severity. This indicates the existence of abnormalities in autonomic cardiac activity within moderate-to-severe OSA, even in the absence of evident cardiac disease. In contrast, we did not determine any significant differences between the patient groups (mild, moderate and severe OSA) in terms of HRT and HRT parameters. These differences in results between the present study and the study by Yang et al.<sup>21</sup> might be attributable to differences in study group selection. Yang et al.<sup>21</sup> grouped their patients as mild and moderate to severe, while we grouped our patients as mild, moderate and severe. In addition, merely one overnight polysomnographic assessment might not provide enough information regarding the severity of OSA. The duration of OSA might also be a factor affecting the deterioration of autonomic cardiac function.

D'Addio et al.<sup>27</sup> investigated the effects of pathological respiratory patterns on HRT among patients with severe OSA. They found that TS increased during apnea but observed decreases during normal intervals following an apnea event (here, OSA patients showed a higher sympathetic tone). This supports the idea that autonomic cardiac function is impaired due to hypoxia during apnea.

Unlike Yang<sup>21</sup> and Ari et al.,<sup>19</sup> Lado et al.<sup>28</sup> found that all HRV parameters decreased during sleep among patients with moderate and severe OSA, compared with a normal, healthy group. In addition, among patients with severe low-frequency band and high-frequency band OSA indices, the total HRV power was lower during intervals labeled as apneas than those labeled as normal. In the present study, although the lowest values for HRV parameters in OSA patients compared with controls were determined; this decrease did not reach statistically significance level among the patient groups. However, we found correlations between some HRV parameters and the values of ODI and AHI. Therefore, these correlations constitute the strength of our research.

The relatively small sample size was a limitation for the present study. Moreover, we only evaluated night-time measurements on HRV and HRT. Thus, further research evaluating both day and night time values is needed in order to contribute important and new data to the literature, given that these parameters are affected by the breathing pattern of OSA patients during sleep. The arrhythmia mechanism in OSA is closely related to apnea and hyperventilation events, which depend on the sympathovagal balance.<sup>29</sup> There is dominance of parasympathetic tone and decreased sympathetic activity during sleep among healthy subjects.<sup>30</sup> However, this situation can change in OSA. Parasympathetic activity, with slowing

of the heart rate, is dominant during periods of apnea. When subsequent apnea termination and temporary arousal from sleep occur, sympathetic activity predominates with resultant heart rate acceleration.<sup>31</sup> Therefore, increased sympathetic tone and baroreflex dysfunction can cause cardiac arrhythmia and sudden death. Sympathetic tone can be evaluated through provocative testing and spectral HRV analysis. The lack of power of the spectral analysis of heart rate and absence of provocative testing are other limitations of the present study. Lastly, HRT parameters could not be calculated in 21% of the patients, who did not present a premature ventricular beat.

## CONCLUSION

HRT and HRV parameters were different in OSA patients than in control subjects. Correlations could be made between the severity of apnea that could be determined through AHI, ODI and total oxygen desaturation, and such parameters seemed to be present. These subjects should be followed up in order to monitor any further adverse outcomes.

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# Trends in mortality from ill-defined causes among the elderly in Brazil, 1979-2013: ecological study

Tendências de mortalidade por causas mal definidas em idosos no Brasil, 1979-2013: estudo ecológico

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## KEY WORDS:

Death certificates.  
Mortality.  
Cause of death.  
Aged.  
Information systems.

## PALAVRAS-CHAVE:

Atestado de óbito.  
Mortalidade.  
Causa de morte.  
Idoso.  
Sistemas de informação.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Mortality measurements are traditionally used as health indicators and are useful in describing a population's health situation through reporting injuries that lead to death. The aim here was to analyze the temporal trend of proportional mortality from ill-defined causes (IDCs) among the elderly in Brazil from 1979 to 2013.

**DESIGN AND SETTING:** Ecological study using data from the Mortality Information System of the Brazilian Ministry of Health.

**METHODS:** The proportional mortality from IDCs among the elderly was calculated for each year of the study series (1979 to 2013) in Brazil, and the data were disaggregated according to sex and to the five geographical regions and states. To analyze time trends, simple linear regression coefficients were calculated.

**RESULTS:** During the study period, there were 2,646,194 deaths from IDCs among the elderly, with a decreasing trend ( $\beta$  -0.545; confidence interval, CI: -0.616 to -0.475;  $P < 0.000$ ) for both males and females. This reduction was also observed in the macroregions and states, except for Amapá. The states in the northeastern region reported an average reduction of 80%.

**CONCLUSIONS:** Mortality from IDCs among the elderly has decreased continuously since 1985, but at different rates among the different regions and states. Actions aimed at improving data records on death certificates need to be strengthened in order to continue the trend observed.

## RESUMO

**CONTEXTO E OBJETIVO:** Medidas de mortalidade são tradicionalmente usadas como indicadores de saúde e são úteis na descrição da situação de saúde de uma população relatando lesões que levam à morte. O objetivo foi analisar a tendência temporal da mortalidade proporcional por causas mal definidas (CMD) em idosos no Brasil entre 1979 e 2013.

**DESENHO E LOCAL:** Estudo ecológico utilizando dados do Sistema de Informação de Mortalidade do Ministério da Saúde no Brasil.

**MÉTODOS:** A mortalidade proporcional por CMD em idosos foi calculada para cada ano da série estudada (1979 a 2013) no Brasil, e os dados foram desagregados por sexo e de acordo com as cinco regiões geográficas e estados. Foi empregado o coeficiente de regressão linear simples para analisar a tendência temporal.

**RESULTADOS:** Durante o período de estudo, houve 2.646.194 mortes por CMD em idosos, com uma tendência decrescente ( $\beta$  -0,545; intervalo de confiança, IC: -0,616 a -0,475;  $P < 0,000$ ) em homens e mulheres. Essa redução também foi observada nas macrorregiões e estados, com exceção do Amapá. Os estados da região Nordeste registraram uma redução média de 80%.

**CONCLUSÕES:** A mortalidade por causas mal definidas em idosos tem diminuído continuamente desde 1985 em ritmos distintos entre as regiões e estados. As ações destinadas a melhorar os registros de dados em certificados de óbito devem ser fortalecidas para dar continuidade na tendência observada.

## INTRODUCTION

Mortality measurements are traditionally used as health indicators<sup>1</sup> and are useful in describing a population's health situation through reporting injuries that lead to death. This allows authorities, among other things, to prioritize the allocation of resources in accordance with the mortality profile identified.<sup>2</sup> Mortality indicators assist in monitoring the trends of the most prevalent causes of death in a population and hence identify which segments are affected to a greater or lesser extent by certain diseases. The numerators of these indicators are obtained from the Mortality Information System (SIM) of the Ministry of Health, which also functions as a strategic tool for management of the healthcare system.<sup>3</sup>

Mortality statistics are only infrequently used. This is partly because of lack of completeness of the data fields that comprise death certificates (DCs), particularly the field representing the underlying cause of death. The lack of information in this field limits the explanatory power of death records regarding mortality patterns in a population.

In situations in which it is not possible to identify the underlying cause of death, such as lack of medical care, failure of doctors to properly maintain assignments and records or missing information, the cause of death is classified as an ill-defined cause (IDC). These correspond to the codes of Chapter XVIII (symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified; codes R00-R99) of the 10<sup>th</sup> Revision of the International Classification of Diseases (ICD-10), and Chapter XVI (symptoms, signs and ill-defined conditions; codes 780-799) of the 9<sup>th</sup> Revision (ICD-9).

High proportions of reported deaths classified as ill-defined causes can significantly alter the mortality rates for specific diseases. This can distort a given community mortality profile and consequently reduce the potential use of these statistics for diagnosing the health of a given population and for planning and administering healthcare services for that population.<sup>4</sup>

By international standards, Brazil was characterized as having high levels of ill-defined causes of death in the middle 1990s.<sup>5</sup> Over the last three decades, the Brazilian government has made significant investments that have improved vital registration systems over recent years.<sup>6,7</sup> The completeness of death counts increased from 80% in 1980-1991 to 95% in 2000-2010, while at the same time the percentage of ill-defined causes of deaths was reduced by about 53% in the country, but with large regional differences. The south and southeast have much better data quality than the rest of the country.<sup>8</sup>

The distribution of ill-defined causes according to demographic characteristics, such as gender and age, is marked by higher incidence among men and the elderly (elderly is defined here as 60 years of age or older). Among the elderly, it is

particularly difficult to identify the cause of death<sup>9</sup> because of the presence of comorbidities (hypertension, diabetes, cancer, arteriosclerosis, dyspnea upon exertion, osteoarthritis and reduced visual acuity, among others) that frequently occur among the elderly. Moreover, age can influence the clinical expression of signs and symptoms,<sup>10</sup> and it may be difficult to deal with the elderly, who may refuse to seek treatment and only do so in the later stages of the disease when there is greater impairment, which can hinder or even prevent establishment of diagnoses. Therefore, it is essential to monitor the quality of the information relating to the underlying cause of death among the elderly and the information relating to the demand for healthcare and social services, so as to better develop care planning and health promotion in this age group.<sup>11</sup>

Mortality trends can be identified from mortality rates in which the risk of death due to a specific cause is measured; or through proportional mortality, in which the relative importance of a disease or group of diseases is reported. In this study, we chose to work with proportional mortality to assess the weight of ill-defined causes of death among the elderly.

## OBJECTIVE

The objective of this study was to analyze the evolution of proportional mortality as a result of ill-defined causes of death among the elderly in Brazil during the period 1979-2013.

## METHODS

This ecological study used time series and exploratory analyses<sup>2</sup> in which secondary data were used. All deaths registered as ill-defined causes among the elderly (detailed in Chapter XVI of ICD-9, for the period between 1979 and 1995; and in Chapter XVIII of ICD-10 from 1996 onwards) were included in this study. This system was implemented between 1975 and 1976, and the computerized database became available for viewing/capture on the web pages of the Information Technology Department of the Brazilian National Health System (DATASUS), with data from 1979 on.<sup>12</sup>

This study used data in the public domain. Thus, there was no need for approval from a research ethics committee. Two spatial scales were used for data analysis: Brazil and its macroregions (north, northeast, south, southeast and center-west). The proportional mortality due to IDCs among the elderly was calculated for each year of the study series (1979 to 2013) in Brazil, and the data were disaggregated according to sex and to the five geographical regions. The proportion of IDC deaths for each sex was calculated based on the total number of deaths for each sex.

Simple linear regression coefficients were calculated to examine the nature and significance of the temporal trend of proportional mortality from ill-defined causes among the elderly.

In this analysis, the variable of time, expressed in years, was entered into the model as the independent variable, and the variable proportions of deaths from IDCs, overall and separated according to gender and geographical region, functioned as the dependent variables. To perform the data analysis, we used Tabwin,<sup>13</sup> which is a public-domain spreadsheet provided by DATASUS, Ministry of Health; and the R software, which is a public-domain statistical package.

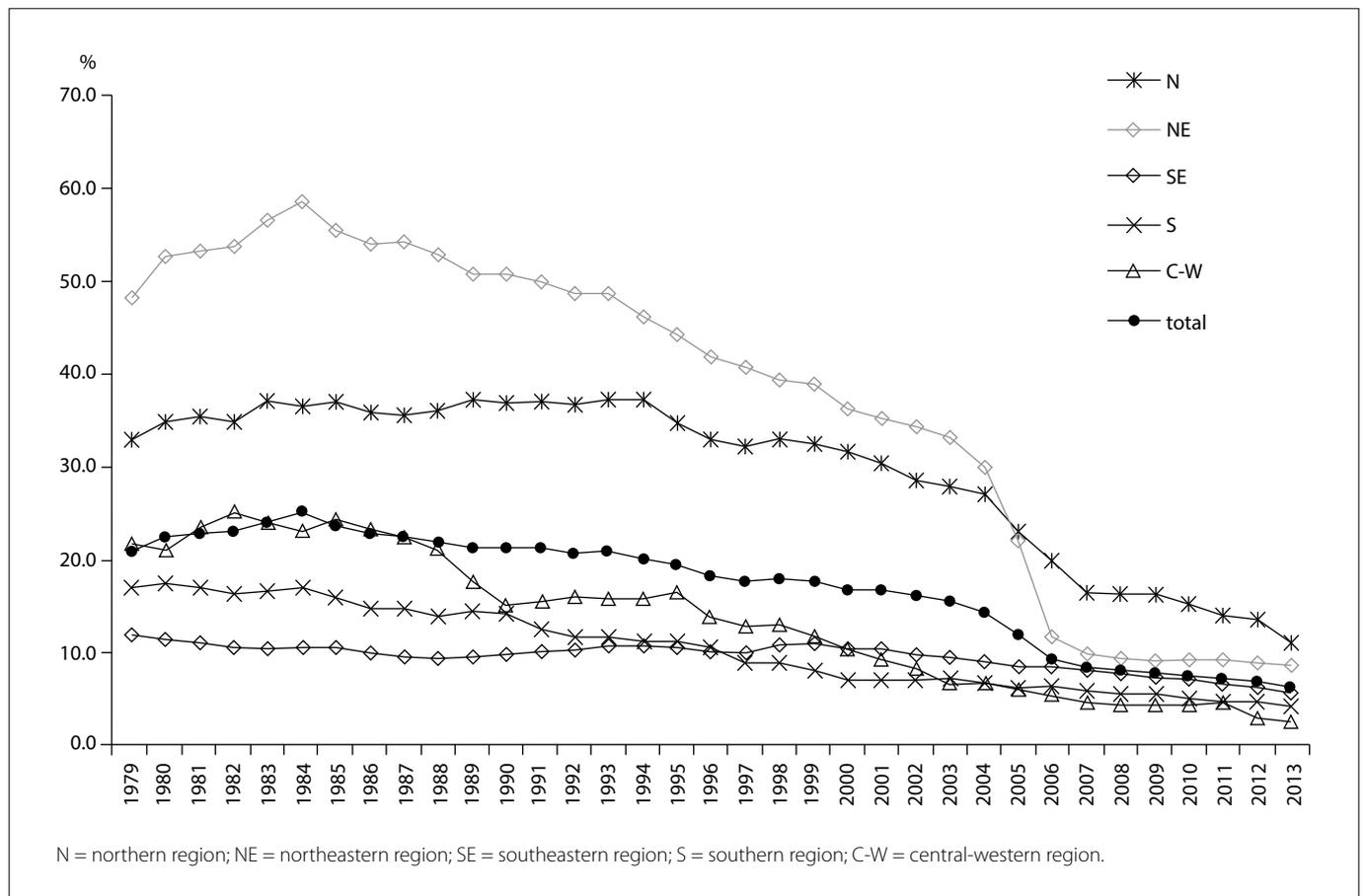
## RESULTS

During the study period, there were 2,646,194 deaths from ill-defined causes among the elderly, corresponding to an average of 75,606 deaths/year. The highest frequency of these deaths (883,162 deaths) occurred in the 1990s, accounting for 33.4% of the total number of deaths. Sex was not reported on 2,943 (0.11%) of the death certificates. There was a significant drop in the proportion of ill-defined causes of death among the elderly for Brazil overall, decreasing from 20.7% in 1979 to 6.2% in 2013 (Figure 1). The highest proportion (25.2%) was recorded in 1984: the underlying cause of death for a quarter of the elderly people who died in

1984 was not identified. In 2005, more than 10.0% of deaths among the elderly were from an unknown underlying cause.

The temporal trend of the proportional mortality from IDCs among the elderly decreased both for Brazil overall ( $\beta$ : -0.545; confidence interval, CI: -0.616 to -0.475;  $P < 0.000$ ) and for the macroregions. In the northeastern region, the proportional mortality from IDCs decreased from 48.1% in 1979 to 8.5% in 2013 ( $\beta$ : -1.584; CI: -1.802 to -1.367;  $P < 0.000$ ); in the central-western region, the proportional mortality from IDCs decreased from 21.7 to 2.6% ( $\beta$ : -0.708; CI: -0.767 to -0.650;  $P < 0.000$ ); in the northern region, the proportional mortality from IDCs decreased from 33.0 to 11.1% ( $\beta$ : -0.725; CI: -0.874 to -0.576;  $P < 0.000$ ); in the southeastern region, the proportional mortality from IDCs decreased from 11.9 to 5.7% ( $\beta$ : -0.123; CI: -0.154 to -0.092;  $P < 0.000$ ); and in the southern region, the proportional mortality from IDCs decreased from 17.1% in 1979 to 4.2% in 2013 ( $\beta$ : -0.427; CI: -0.452 to -0.402;  $P < 0.000$ ).

In the northeastern region, between the years 1980 and 1990, more than 50.0% of deaths among the elderly were classified as IDC, reaching a peak of 58.5% in 1984; this proportion was



**Figure 1.** Proportion of deaths from ill-defined causes among the elderly, in relation to the total number of deaths recorded for the elderly, in Brazil overall and in its macroregions, 1979-2013.

5.6 times higher than that in the southeast (10.5%) in 1984. Since 1997, IDC deaths have accounted for less than 10.0% of the total number of deaths among the elderly in the south; this occurred ten years later in the northeast (in 2007).

In 2004, the northeastern region recorded the highest proportion of deaths from IDCs. In 2005, the highest proportion of deaths occurred in the northern region. This region was the only one to record a proportion greater than 10.0% in the last year of the study: in 2013, the proportion of deaths from IDCs among the elderly in the northern region was 11.1%, while the national average was 6.2%.

The distribution according to sex showed similar patterns for men and women. The proportion of IDCs increased from 1979 until 1984, when it reached a peak of 25% for both sexes, followed by a decreasing trend extending until the last year of the study, when it reached 6.2%. The trend showed a decrease for both males ( $\beta$ : -0.549; CI: -0.618 to -0.479;  $P < 0.000$ ) and females ( $\beta$ : -0.540; CI: -0.613 to -0.467;  $P < 0.000$ ). Since 2006, the proportion of deaths due to IDCs among the elderly has remained below 10.0% in both sexes (Figure 2).

Table 1 shows that in two states, Roraima and Amapá, which are both located in the north, there was an increase in the

proportion of deaths from IDCs among the elderly between the years 1996 (when ICD-10 started to be used) and the latest year for which mortality data were available on the DATASUS website. There were reductions in all the other states, particularly in the states of Tocantins in the northern region, Rio Grande do Norte in the northeastern region and Espírito Santo in the southeastern region, which had reductions of more than 90%. In 2013, only four states had rates that exceeded 10% (Amazonas, Pará and Amapá in the north and Bahia in the northeastern region).

The proportion of deaths from ill-defined causes among the elderly, within the total number of IDC deaths registered in Brazil during the period 1979-2013, displayed an upward trend with minor fluctuations, increasing from 37.8% in 1979 to 64.0% in 1997 and reaching 66.6% in 2013 (Figure 3).

## DISCUSSION

The time series analysis on the proportional mortality from ill-defined causes among the elderly revealed a marked and progressive decrease during the study period. This reduction was observed for the country as a whole, with regional variations that were accentuated in the north-south direction, ranging from a reduction of approximately 95.5% in the state of Espírito Santo,

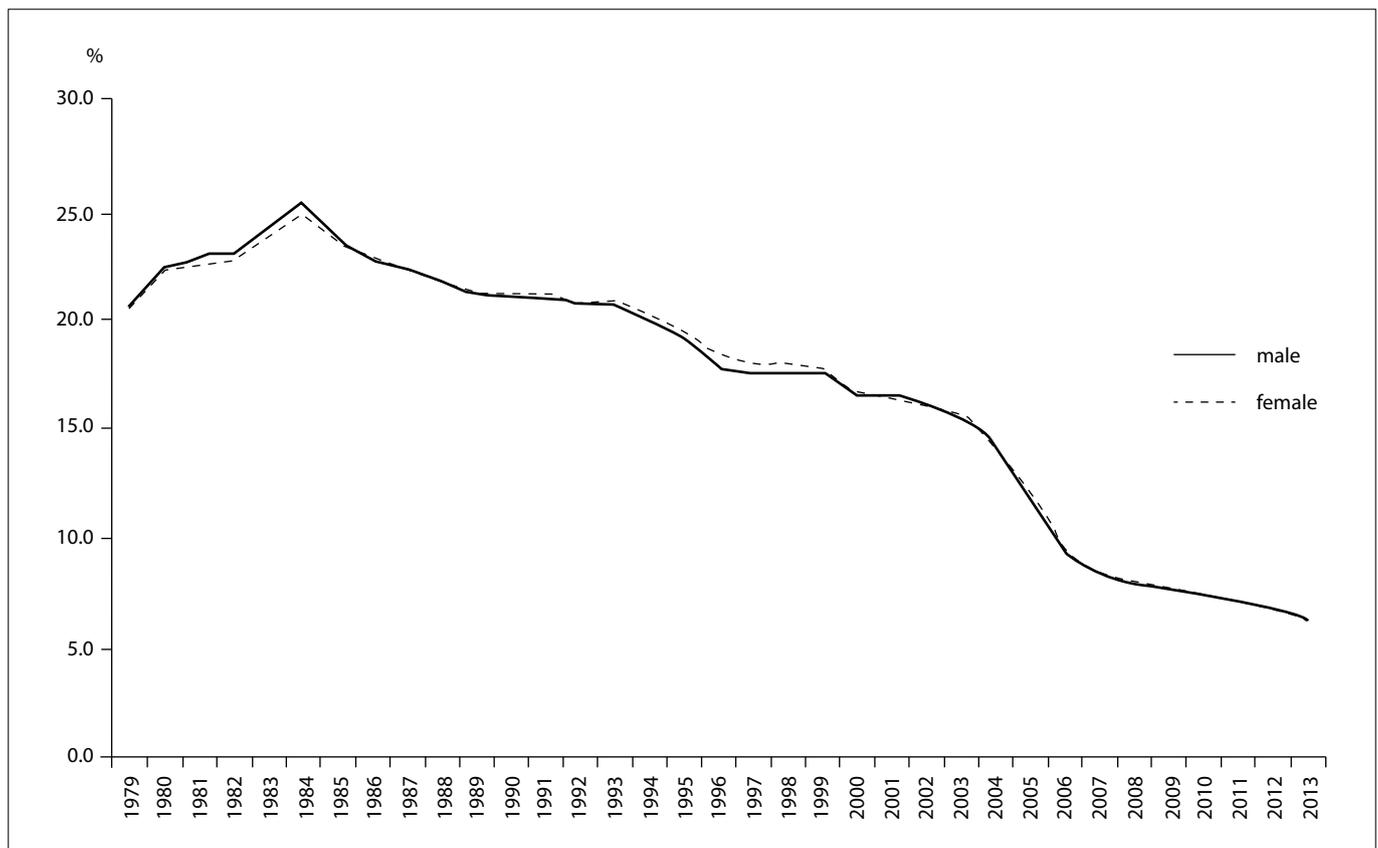


Figure 2. Proportion of deaths from ill-defined causes among the elderly according to sex, Brazil, 1979-2013.

**Table 1.** Proportional mortality from ill-defined causes among the elderly according to macroregions and states in selected years (1996 and 2013)

Macroregion/ states	1996		2013		2013- 1996*
	Total deaths	% Ill-defined	Total deaths	% Ill-defined	
Northern region	15670	33.1	36322	11.1	-66.5
Roraima	1638	26.8	3979	7.4	-72.2
Acre	860	35.7	1711	9.5	-73.5
Amazonas	3009	31.7	7421	17.9	-43.4
Roraima	286	5.6	793	7.3	+30.7
Pará	7833	35.4	17391	11.0	-69.0
Amapá	465	8.2	1120	12.6	+54.1
Tocantins	1579	41.7	3907	3.2	-92.3
Northeastern region	106272	41.9	192312	8.5	-79.7
Maranhão	5771	50.5	17234	7.3	-85.5
Piauí	4055	44.3	11371	5.3	-88.0
Ceará	14535	42.6	32023	7.1	-83.3
Rio Grande do Norte	6840	40.6	11992	3.4	-91.7
Paraíba	10149	59.9	17174	7.0	-88.4
Pernambuco	24908	33.8	36897	4.9	-85.4
Alagoas	6793	51.5	10634	7.2	-86.1
Sergipe	4017	48.1	6994	7.2	-85.1
Bahia	29204	37.5	47993	15.7	-58.1
Southeastern region	247102	10.1	366939	5.7	-43.7
Minas Gerais	52902	15.9	81909	8.0	-49.8
Espírito Santo	8445	24.7	13018	0.9	-96.2
Rio de Janeiro	62942	9.9	86348	5.0	-50.0
São Paulo	122813	6.7	185664	5.3	-20.1
Southern region	86758	10.5	128148	4.2	-60.2
Paraná	29672	11.6	45820	3.9	-66.5
Santa Catarina	15494	19.1	23887	3.7	-80.7
Rio Grande do Sul	41592	6.6	58441	4.6	-29.6
Central-western region	21963	13.9	44694	2.6	-81.4
Mato Grosso do Sul	5064	13.4	9002	1.4	-89.4
Mato Grosso	3167	15.4	8433	5.6	-63.7
Goiás	10473	17.5	20830	2.5	-85.9
Federal District	3259	1.4	6429	0.6	-55.1
<b>Total</b>	<b>477765</b>	<b>18.2</b>	<b>768415</b>	<b>6.2</b>	<b>-65.8</b>

Source: Mortality Information System (SIM), Health Situation Analysis Department, Health Surveillance Secretariat, Ministry of Health.

\*Percentage change 2013-1996  $\{(t_1 - t_0)/t_0 * 100\}$ .

which is located in the southeastern region, to an increase of 147.8% in Amapá in the northern region. The largest decreases were observed in the states of the northeastern region, which reported an average decrease of more than 80.0%, except for the state of Bahia (60.4%).

The geographic variation in this indicator can be partially attributed to the different levels of economic development presented by the federal states, the care structure provided for the

population, the structure and organization of health information record systems, the ease of access to healthcare services and the effects from improving qualification-oriented programs.

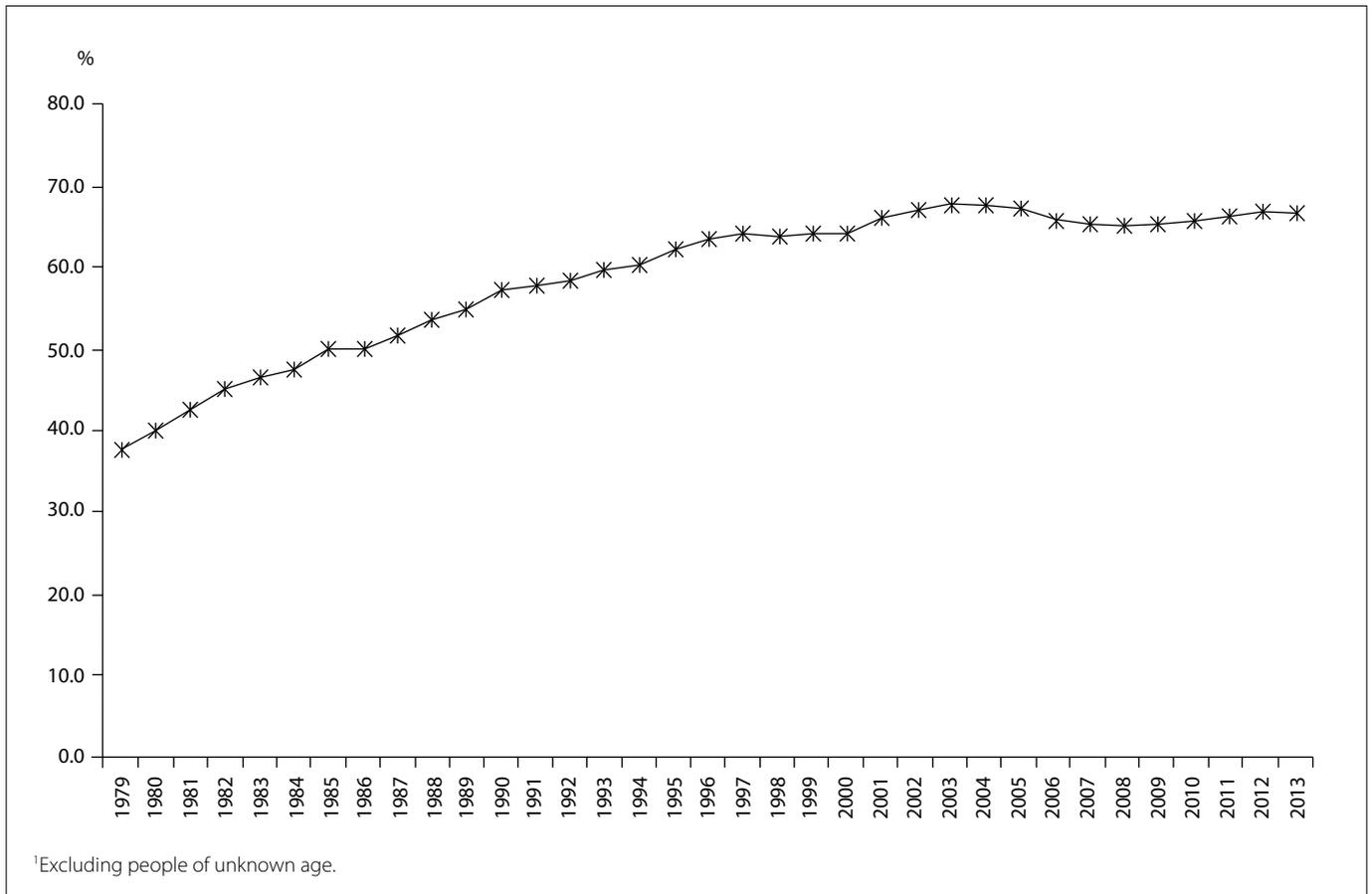
A study conducted in the state of São Paulo that evaluated health information<sup>14</sup> identified significant regional health variations in relation to ill-defined causes of death among the elderly. The proportional mortality from ill-defined causes of death for the state in 2010 was 5.6%, ranging from 1.0% in the greater ABC region to 19.4% in the central DRS II region. The significant regional health differences observed in the state of São Paulo reflect deep inequalities in living conditions, which are closely related to social and economic factors and have a major influence on the quality of vital statistics records.<sup>15</sup>

Although occurrences of IDCs among the elderly have displayed a significant reduction, they remain high compared with other countries. In the period between 2002 and 2006, IDC deaths in the general population accounted for 1.5% of deaths in Colombia.<sup>16</sup> In the United States, IDCs in the general population accounted for less than 2.0% of all deaths,<sup>17</sup> and in 2003 in Chile, the percentage of deaths recorded under this classification was 2.8%.<sup>18</sup> The pattern observed in these countries differs greatly from that found in South Africa, where the proportion of ill-defined causes of death increased from 12.2% in 1999 to 13.9% in 2007.<sup>19</sup>

Keer-Pontes and Rouquayrol<sup>20</sup> stated that deaths from ill-defined causes reflect “not only worse quality of life and health of the population, but also lower quality or lack of medical care provided to that population”. They also reported that in cases in which the deaths received a clinical follow-up in the final stages of the disease, poor completion of the DC was partly related to diagnostic errors as a result of lack of technical resources or personnel deficiencies, ignorance of the correct way to complete a DC, bureaucratic issues and attention to family prejudices against stigmatizing diseases (syphilis, AIDS and alcoholism).

Investigations that have assessed the quality of DC data show that the vast majority of deaths categorized as from ill-defined causes result from doctors incorrectly completing the DC.<sup>9</sup> Adequately diagnosed cases are reported using terms that are vague or poorly defined, such as “cardiac arrest” and “multiple organ failure”, which under coding rules are classified in Chapter XVIII of ICD-10.<sup>9</sup>

Since 2005, the Brazilian government has focused on helping states and municipalities from the poorest regions (north and northeast) through targeting increased completeness and reduction of ill-defined causes of death. This effort produced an important decrease in the proportion of ill-defined causes from all regions over time, especially in 2006-2010, with improvements in terms of both magnitude and reduction of differentials across regions.<sup>21</sup>



**Figure 3.** Proportion of deaths from ill-defined causes among the elderly in relation to the total number of deaths registered as having ill-defined causes,<sup>1</sup> Brazil, 1979-2013.

The downward trend in the proportion of this type of death is widespread, but we believe that peculiarities are maintained in some age groups such as the elderly. The high occurrence of home deaths in this age group<sup>9</sup> also increases the chance of the death being classified as having an ill-defined cause. A study conducted in four state capitals that assessed mortality from ill-defined causes among the elderly from 1996 to 2007 found that in Porto Alegre, 50% of deaths classified as IDCs occurred at home.<sup>22</sup> In the state of São Paulo in 2010, 48.2% of these events occurred at home, and only 44.2% occurred in hospitals or other healthcare facilities. Moreover, unattended deaths, which are one of the most common situations for ill-defined causes of death, represented 31% of all ill-defined causes of death. These deaths occur predominantly at home (42.6%).<sup>14</sup>

Moreover, the classification of deaths did not differ according to sex. The downward trend in both sexes suggests that the factors that caused this reduction produced the same effects in both sexes.

The high proportions of IDC deaths observed in the 1980s may reflect a time when the need for services and healthcare professionals to assist the population was greatest. This need resulted

from uneven spatial distribution of healthcare services and professionals in Brazil, which were primarily located in the southern and southeastern regions and in major urban centers.

The above mentioned problems added to the difficulty of the population's access to healthcare services and the organization of health surveillance services.<sup>23</sup> The disabilities of the organization of health surveillance services depicts a situation of serious neglect of a problem regarding information that was more marked that decade, thus reflecting a failure to comply with the mandatory registration of vital events, and specifically deaths, and the lack of importance given to this by those in charge of planning healthcare actions.

The household living situations of the elderly, whether in rural or urban areas, may explain the resistance to or greater difficulty in health service provision. The predominantly rural location pattern probably affects the demand for healthcare because rural populations have less access to and therefore make less use of healthcare services.<sup>24,25</sup> This may result partly from transportation difficulties, financial constraints and greater resistance to seeking medical care.

We believe that seeking medical care was a more important issue in the mid-1980s. A significant proportion of the population over 60 years of age during that decade came from a cohort that was primarily born in rural areas, and a fraction of that population is still alive today. Brazil was historically a country with predominantly rural characteristics, but since the 1950s, Brazil has been undergoing a transformation into a more urbanized country. Only in the 1960s did the urban population exceed the rural population.<sup>26</sup> The low frequency of healthcare services use among people living in rural areas throughout their lives is a behavioral characteristic that may change as these people become older, given that the demand for healthcare services can be expected to increase. This increase in the frequency of healthcare services use among the elderly has been previously demonstrated. This stage of life is characterized by a greater biological vulnerability associated with higher prevalence of diseases and disabilities.<sup>27</sup>

The cohorts born in the 1930s and subsequently differed from those that preceded them in relation to household status at birth. Some of those who were born in the countryside migrated into cities, and this pattern became more pronounced in the 1950s and 1960s, and extended into the early 1990s. According to the Brazilian Institute for Geography and Statistics (IBGE) (2001),<sup>26</sup> the proportion of the population living in urban areas increased from 67.5% in 1980 to 75.5% in 1991 and 81.2% in 2000, partly because of the intense rural-urban migration process.

This population has had more experience with urban standards in relation to healthcare and seeking treatment. This new social integration has resulted in increased demand for healthcare and has coincided with a period of intensifying public campaigns addressing various healthcare service issues, such as the Elderly Vaccination Campaign, in which people aged 65 year and older were immunized against influenza, beginning in 1999. In 2000, the campaign began offering immunization to those over 60 years old. Campaigns towards the elderly may have contributed towards encouraging them to seek healthcare services, thus reducing the culturally constructed resistance.

The availability of healthcare services and professionals prepared to meet the needs of this contingent, which swells the population, is a challenge for both the state and society. Populations have the ability to extend their average lifespan and therefore age is an indicator of social evolution, which is influenced by the pattern of economic development and the technical/scientific attainment level of the society to which the population belongs. Such achievements are a source of concern for both society and the state, which need to adjust to new demands, and they have an impact on the economic and social structure. The challenge ahead for the twenty-first century is to provide quality-of-life support to a growing elderly population of primarily low socioeconomic and educational level and high prevalence of chronic diseases and disabilities.<sup>28,29</sup>

Apart from these unwieldy problems, the reduction in the proportion of ill-defined causes of death points towards the possibility of achieving an even lower level if the ongoing actions are intensified. The Brazilian states with the worst indicators need to be prioritized, so as to identify the main causes of the poor quality of information and implement a series of actions to reverse this situation. Among the measures that could help reduce occurrences of deaths categorized as having ill-defined causes is continuous monitoring of what is causing death in this age group, with training and skill transfers for municipalities with greater difficulties, with the aim of reaching physicians in these regions and encouraging them to fill out the underlying cause of death on the death certificate.

This study was based on large spatial units, including macroregions and states, for the data analysis. Although this allowed approximation of occurrences and the spatial distribution of the event analyzed, the spatial unit size can be considered to be a limitation of this study. Use of smaller spatial units, such as regional health districts or even municipalities, would provide knowledge in greater detail, including identification of the localities with major problems in classifying deaths, and would allow interventions to be targeted to the most deprived locations.

## CONCLUSIONS

Proportional mortality from ill-defined causes among the elderly was seen to present a marked progressive decrease during the study period. This reduction was observed for the country as a whole, with regional variations accentuated in the north-south direction. These variations require geographically differentiated interventions in order to reduce their occurrence. Thus, improving the quality of mortality statistics among the elderly is essential in order to provide valid and reliable data for producing information to support healthcare planning for this group of elderly individuals.

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# Transcranial direct current stimulation for treatment-resistant obsessive-compulsive disorder: report on two cases and proposal for a randomized, sham-controlled trial

Estimulação transcraniana por corrente contínua para o transtorno obsessivo compulsivo resistente ao tratamento: relato de dois casos e proposta de um ensaio clínico randomizado e controlado por *sham*

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## KEY WORDS:

Obsessive-compulsive disorder.  
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Electric stimulation.  
Transcranial direct current stimulation.

## PALAVRAS-CHAVE:

Transtorno obsessivo-compulsivo.  
Terapia por estimulação elétrica.  
Eletrodos.  
Estimulação elétrica.  
Estimulação transcraniana por corrente contínua.

## ABSTRACT

**CONTEXT AND OBJECTIVE:** Neuromodulation techniques for treating obsessive-compulsive disorder (OCD) have expanded through greater understanding of the brain circuits involved in this disorder. Transcranial direct current stimulation (tDCS), a non-invasive technique, has been studied as an alternative for treatment-resistant OCD. We describe the design of a clinical trial using tDCS for OCD and report on the outcomes from two patients with primary OCD who were resistant to cognitive-behavioral therapy and to selective serotonin reuptake inhibitors, and who received tDCS in an open manner during the training phase for the study procedures.

**DESIGN AND SETTING:** Methodological description of a clinical trial using tDCS for treatment-resistant OCD at a university hospital; and a report on two cases.

**METHODS:** The proposed study is randomized, sham-controlled and double-blind. Forty-four patients will be randomized to either active or sham intervention. The active intervention consists of applying an electric current of 2 mA, with the cathode positioned in the region corresponding to the supplementary motor cortex (bilaterally) and the anode positioned in the deltoid. The primary outcome will be the reduction in baseline YBOCS (Yale-Brown Obsessive Compulsive Scale) score at the end of week 4. The secondary outcomes will be depression and anxiety symptoms. Genetic markers, cortical excitability and neurocognitive performance will be investigated.

**RESULTS:** The first patient showed significant improvement, whereas the second remained symptomatic after four weeks and after six months. tDCS was well tolerated.

**CONCLUSION:** tDCS for treatment-resistant OCD merits randomized controlled trials that test its effectiveness.

**CLINICAL TRIAL REGISTRATION:** NCT02743715.

## RESUMO

**CONTEXTO E OBJETIVO:** Técnicas de neuromodulação para o tratamento do transtorno obsessivo compulsivo (TOC) vêm se expandindo com o melhor entendimento dos circuitos cerebrais envolvidos no transtorno. A estimulação transcraniana por corrente contínua (ETCC), uma técnica não invasiva, vem sendo estudada como alternativa para o TOC resistente aos tratamentos convencionais. Descrevemos o desenho de um ensaio clínico utilizando a ETCC para o TOC e relatamos os desfechos de dois pacientes com TOC primário resistentes à terapia cognitivo-comportamental e aos inibidores seletivos de recaptura da serotonina, que receberam ETCC de modo aberto durante a fase de treino dos procedimentos do estudo.

**TIPO DE ESTUDO E LOCAL:** Descrição metodológica de um ensaio clínico utilizando ETCC para o TOC resistente num hospital universitário e relato de dois casos.

**MÉTODOS:** O estudo proposto é randomizado, controlado por *sham* e duplo-cego. 44 pacientes serão randomizados para intervenção ativa ou simulada (*sham*). A intervenção ativa consiste em aplicar uma corrente elétrica de 2 mA, com cátodo posicionado na região correspondente à área cortical motora suplementar (bilateralmente) e ânodo posicionado no deltoide. Desfecho primário: redução do escore inicial da escala YBOCS (Yale-Brown Obsessive Compulsive Scale) ao final da quarta semana. Desfechos secundários: sintomas depressivos e ansiosos. Marcadores genéticos, excitabilidade cortical e performance em testes neurocognitivos serão investigados.

**RESULTADOS:** O primeiro paciente apresentou melhora significativa, enquanto o segundo permaneceu sintomático ao término das quatro semanas e após seis meses. A ETCC foi bem tolerada.

**CONCLUSÃO:** A ETCC para o tratamento do TOC resistente merece ensaios clínicos randomizados que testem sua efetividade.

**REGISTRO DE ENSAIO CLÍNICO:** NCT02743715.

## INTRODUCTION

Obsessive-compulsive disorder (OCD) is an often-chronic and potentially disabling condition with a prevalence of 2-3% in the general population,<sup>1-3</sup> characterized by obsessions (unwanted repetitive thoughts and images) and compulsions (repetitive behavior usually adopted to alleviate the discomfort elicited by the obsessions). OCD is frequently associated with other psychiatric conditions such as mood and anxiety disorders.<sup>2</sup> The impairment relating to OCD affects personal, social and occupational functioning, and it thus leads patients and their families to poorer quality of life, to an extent that is similar to what is seen in relation to schizophrenia and mood disorders.<sup>4-7</sup>

The first-line treatments for OCD include use of the serotonin reuptake inhibitor (SRI) clomipramine, selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT). However, about one third of patients fail to experience significant improvement after these first-choice treatments.<sup>8</sup> Augmentation of SRI use with CBT or antipsychotics has been reported to increase the response rates, but a considerable number of patients remain significantly ill.<sup>9</sup>

Therapeutic alternatives involving neuromodulation have been considered for cases of treatment-resistant OCD. There is evidence that OCD is associated with dysfunction in the frontal-striatum-pallidum-thalamic circuitry, including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortices, supplementary motor area (SMA), anterior cingulate gyrus and basal ganglia.<sup>10,11</sup> Neuromodulation techniques targeting these routes may be invasive, such as deep brain stimulation; or noninvasive, e.g. repetitive transcranial magnetic stimulation<sup>12</sup> and transcranial direct current stimulation (tDCS).<sup>13</sup>

tDCS consists of applying a direct electric current across two relatively large electrodes: the cathode and the anode. This current is able to penetrate the skull and reach the cerebral cortex, thereby modifying the neuronal membrane resting potential<sup>14,15</sup> and modulating the neuronal firing rates. In fact, tDCS increases cortical excitability without inducing an action potential.<sup>16</sup> It has shown promising results for depression and schizophrenia, with a favorable safety and tolerability profile.<sup>17,18</sup>

With regard to OCD, Narayanaswamy et al. reported two cases of SSRI-refractory patients who received 20 sessions of tDCS at 2 mA, with 40% improvement.<sup>19</sup> In another open-label study, eight treatment-resistant OCD patients received 10 sessions of tDCS at 2 mA. Five of them showed at least 25% improvement in baseline Y-BOCS (Yale-Brown Obsessive Compulsive Scale) scores and three of them showed at least 35% improvement.<sup>20,21</sup> These small heterogeneous open studies suggest that tDCS may be effective for OCD.

## OBJECTIVE

Thus, the aim of the present paper was to report on the outcomes of two patients whose primary disorder was OCD. They had been

unresponsive to cognitive-behavioral therapy and/or SSRIs or clomipramine, and they received 20 sessions of tDCS during the pilot phase of a randomized clinical trial (RCT). First, we describe the methodology and then we assess the efficacy and safety of tDCS for treating OCD. The intervention delivered to the two patients reported on was identical to that described below.

## METHODS

### Design

This is a randomized, double-blind, sham-controlled trial. After randomization, all subjects will receive 20 daily sessions of 30 minutes duration of either tDCS or a sham intervention for four weeks (Mondays through Fridays). Follow-up assessments will take place at weeks 4, 6, 9 and 12. All subjects and staff members will be blind to the treatment condition, except for the registered nurse and an attending physician at the Neuromodulation Unit who will conduct the sessions and are not members of the research team. The project has been approved by our institution's Research Ethics Committee (1.015.347) and is registered at ClinicalTrials.gov (NCT02743715).

### Sample and eligibility

There are no controlled clinical trials that assess tDCS for treating OCD. Therefore, the sample size calculation will be based on the repetitive transcranial magnetic stimulation (rTMS) for OCD studies available in the current literature, due to the proximity of the intervention model, sample characteristics and outcome measurements. Thus, based on one meta-analysis,<sup>22</sup> which found that active rTMS was more favorable than sham intervention, with Hedges *g* of 0.59 ( $z = 2.73$ ;  $P = 0.006$ ) for a two-tailed  $P$  of 0.05 and a power of 95%, the total sample size is 33 subjects. Taking an attrition rate of approximately 30%, we estimated that the final sample size should be 44 patients. The patients will be recruited from the OCD Spectrum Disorders Program at the Institute of Psychiatry, University of São Paulo Medical School.

The inclusion criteria are: age 14-65 years; a primary DSM-5<sup>23</sup> diagnosis of OCD and a baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score greater than or equal to 16.<sup>21</sup> The presence of psychiatric comorbidities will be allowed, provided that OCD is the primary disorder. Up to two failed previous pharmacological treatment methods (SSRIs and SSRIs combined with anti-psychotics) and CBT will be allowed. Subjects who have failed these three treatment methods will not be admitted into the study. Current use of medication will be permitted, as long as the doses have been stable for at least six weeks.

The exclusion criteria comprise presence of severe suicidal ideation (structured plan for suicide or attempted suicide within the past four weeks); bipolar disorder; substance abuse/dependence;

schizophrenia or psychotic disorders; dementia; pregnancy; or specific contraindications for tDCS (metal plates on the head or anatomical abnormalities).

### Staff

A registered nurse trained in the procedures of tDCS sessions will be the person to take care of the patient from his/her arrival at the facility until discharge. She will accompany the patient through the tDCS sessions and will be allowed to operate the tDCS device under medical supervision. These two members of the team will be the only non-blind staff in the study. The other members of the team will be two clinical psychiatrists, who will be responsible for recruitment, computerized randomization and the medical appointments over the course of the study; and a research assistant with a degree in psychology who will be responsible for the baseline and 12<sup>th</sup> week assessments.

### Interviews

The following instruments will be used: demographic and socio-economic (ABIPEME)<sup>24</sup> forms, personal and family medical histories, and the following questionnaires: Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS),<sup>25</sup> Y-BOCS, Sensory Phenomena Scale (USP-SPS),<sup>26</sup> Beck Depression Inventory (BDI),<sup>27</sup> Beck Anxiety Inventory (BAI),<sup>28</sup> Brown Assessment of Beliefs Scale,<sup>29</sup> Clinical Global Impression-Improvement subscale (CGI),<sup>30</sup> World Health Organization Quality of Life assessment (WHOQOL-100),<sup>31</sup> and Structured Clinical Interview for DSM-4 (SCID-I).<sup>32</sup> It should be noted that the SCID for DSM-5 is not currently available or validated in the Portuguese language. Therefore, our strategy will be to have the subjects interviewed by trained clinicians using the SCID-IV and then to make diagnoses by means of the DSM-5 criteria, using clinical experience to move between the two instruments.

### Intervention

The intervention will consist of stimulation by means of a direct electrical current to the cathode, which is positioned in the area corresponding to the bilateral supplementary motor cortex. The anode is positioned in the left deltoid (neutral region). Our choice for the location of the electrodes was based on the findings of Senço et al.<sup>33</sup> In their systematic review, it was found that placing the cathode on the pre-SMA and the anode in the extra-cephalic area seemed to activate most of the areas relating to OCD, based on computerized head modeling analysis on electrode positioning in transcranial magnetic stimulation and deep brain stimulation trials on OCD.

The current strength will be 2 mA on a surface of 25 cm<sup>2</sup>, applied in 30-minute daily sessions for 20 consecutive weekdays. In the sham group, the device will be turned off after 30 seconds

of active stimulation. This is a blinding method that has been used previously to induce the same sensations as in active stimulation, like mild tingling on the skin.<sup>34</sup>

### Outcomes

The primary outcome will be the reduction in baseline YBOCS scores at the end of the fourth week. The secondary outcomes will include measurements of depression and anxiety symptoms. To evaluate patients treated in an open manner, a follow-up will be conducted six months afterwards in order to assess the long-term effect of the intervention.

### Tolerability

Any adverse effects from tDCS will be measured by means of the Systematic Assessment for Treatment Emergent Effects (SAFTEE) and the tDCS adverse events questionnaire.<sup>35,36</sup>

### Case reports

A preliminary, open phase of the proposed trial was conducted to enable implementation of the study routines, and to test the tolerability of the procedures and train the staff in the study procedures. Two patients with severe treatment-resistant OCD received the tDCS intervention as described above in the intervention section. It should be noted that, differing from the inclusion criteria of the proposed study, the two patients described below had histories of failure in more than two SSRI trials. Both of them tolerated the study procedures well. The first patient maintained his severe symptoms, whereas the second showed significant improvement, which was maintained over time.

- Case 1: This patient was a 37-year-old married businessman with incomplete higher education. He had been diagnosed with OCD, comorbid social phobia and generalized anxiety disorder at the age of 16 years. His illness was characterized by a need for symmetry, ordering, counting and arranging. The symptoms had worsened over time and, despite his own efforts, he was unable to control them, which had led to impairment of his relationships and social life. A lot of effort was required from him to meet his objectives at work. Therapeutic failures with SSRIs and side effects from drugs added to his suffering. He had never required hospitalization and had no family history of OCD. At the time of admission, he was taking fluoxetine (100 mg/day). His YBOCS scores were 38 (0% improvement) at baseline, 38 (0%) at four weeks, 38 (0%) at twelve weeks and 31 (18% improvement), six months after completing the intervention, with no significant changes in depression or anxiety symptoms.
- Case 2: This patient was a 31-year-old unemployed man with incomplete higher education who was living with his parents. He had been diagnosed with OCD at the age of 19 years, with comorbid depressive symptoms and a lifetime history

of psychotic (paranoid) symptoms, for which he had required hospitalization. He had received electroconvulsive therapy for depressive symptoms and had used marijuana and cocaine. His OCD was characterized by contamination/cleaning and aggression symptoms. As a result of the symptoms, the patient could not keep a job or complete university, and he depended on his parents. Previous treatments with SSRIs and combinations of SSRIs and neuroleptics were unsuccessful. He had completed 20 sessions of CBT, with partial improvement that was not maintained over time. At the time of recruitment he was taking escitalopram (30 mg/day), risperidone (2 mg/day), clozapine (400 mg/day) and valproic acid (500 mg/day). His YBOCS scores were 40 at baseline, 33 (17% improvement) at 12 weeks and 18 (55% improvement), 6 months after completion of tDCS. There were 50% reductions in both the BDI and the BAI scores.

## DISCUSSION

The aims of this study were to describe the methods of a controlled trial of tDCS for treatment-resistant OCD and to report on the outcomes from two patients with treatment-resistant OCD who were treated in an open manner with tDCS. One patient showed minimal improvement over time, with a 19% reduction in baseline YBOCS score, six months after completion of tDCS, whereas the other patient showed a significant improvement at completion of the treatment, which was maintained six months later (45% reduction in baseline YBOCS score).

In line with the results from our second patient, three previous open studies presented promising results for tDCS. Bation et al. reported improvements of at least 25% in five out of their eight patients and 35% in three of them.<sup>20</sup> Narayanaswamy et al. reported a 40% improvement in two cases and D'Urso et al. reported a 30% improvement in one subject.<sup>19,37</sup> With regard to improvement of depression and anxiety symptoms, which were prominent in our second patient, the same observation was reported by Narayanaswamy et al.<sup>19</sup> Unlike in our study, Bation et al. excluded patients with additional psychiatric diagnoses, whereas D'Urso et al. did not assess the outcomes of mood or anxiety.<sup>20,37</sup>

It should be noted that the extant studies differ in the positioning of the electrodes. Bation et al. located the cathode over the left OFC and the anode over the right cerebellum; Narayanaswamy et al. placed the anode on the left pre-SMA/SMA and the cathode over the right supraorbital area; and D'Urso et al. placed the active electrode on the pre-SMA and the neutral electrode on the right deltoid.<sup>19,20,37</sup> Therefore, the ideal positioning of the electrodes is still a matter of debate.

## CONCLUSIONS

In conclusion, our observation on the two cases reported here was that a trial of 20 consecutive, 30-minute sessions of tDCS at

2 mA was well tolerated. By running a randomized, double-blind, sham-controlled trial, we intend to further clarify several questions regarding the effectiveness of tDCS for treatment-resistant OCD patients, including factors associated with the short and long-term response and the role of psychiatric comorbidities in the outcomes.

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# Severe lower urinary tract symptoms due to anteriorly located midline prostatic cyst arising from the bladder neck in a young male: case report

Sintomas graves do trato urinário inferior em decorrência de cisto anteriormente localizado na linha mediana da próstata proveniente do colo vesical em um jovem do sexo masculino: relato de caso

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## KEY WORDS:

Cysts.  
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Urinary bladder neck obstruction.

## PALAVRAS-CHAVE:

Cistos.  
Próstata.  
Doenças prostáticas.  
Bexiga urinária.  
Obstrução do colo da bexiga urinária.

## ABSTRACT

**CONTEXT:** Prostatic cysts are uncommon. These cysts are usually asymptomatic and are diagnosed incidentally during ultrasonographic examination. On rare occasions, they may cause drastic symptoms.

**CASE REPORT:** We report on a case of severely symptomatic anteriorly located prostatic cyst arising from the bladder neck in a 30-year-old man presenting with lower urinary tract symptoms, without clinical evidence of benign prostatic hyperplasia. Transrectal ultrasonography (TRUS), computed tomography (CT) and cystourethroscopy demonstrated a projecting prostatic cyst that occupied the bladder neck at the precise twelve o'clock position. It was acting as a ball-valve, such that it obstructed the bladder outlet. Transurethral unroofing of the cyst was performed and the patient's obstructive symptoms were successfully resolved. Histopathological examination indicated a retention cyst.

**CONCLUSIONS:** It should be borne in mind that midline prostate cysts can be a reason for bladder outlet obstruction in a young male. Such patients may have tremendous improvement in symptoms through transurethral unroofing of the cyst wall.

## RESUMO

**CONTEXTO:** Cistos prostáticos são incomuns. Esses cistos são geralmente assintomáticos e são diagnosticados incidentalmente durante o exame ultrassonográfico. Raramente podem causar sintomas importantes.

**RELATO DE CASO:** Relatamos um caso sintomático de grave cisto prostático de localização anterior, originário do colo da bexiga de um homem de 30 anos de idade, que apresentou sintomas do trato urinário inferior, sem evidência clínica de hiperplasia prostática benigna. Ultrassonografia transretal (TRUS), tomografia computadorizada (CT) e cistoureoscopia demonstraram um cisto prostático saliente que ocupou o colo da bexiga na posição exata de 12 horas. O cisto estava agindo como uma válvula de esfera, obstruindo a saída da bexiga. Retirada da cobertura do cisto foi realizada por via transuretral e os sintomas obstrutivos do paciente foram resolvidos com sucesso. O exame histopatológico indicou um cisto de retenção.

**CONCLUSÕES:** Deve ser lembrado que a linha média do cisto de próstata pode ser motivo de obstrução da saída da bexiga em um jovem do sexo masculino. Esses pacientes podem ter notável melhoria nos sintomas com retirada da cobertura por via transuretral da parede do cisto.

## INTRODUCTION

Over recent years, the widespread availability of transrectal ultrasound (TRUS), computed tomography (CT) and magnetic resonance imaging (MRI) has led to increased frequency of diagnoses of incidental prostatic cysts. The majority of prostatic cysts are asymptomatic and originate in the posterior area of the prostate, such as in the Müllerian ducts and the utricle, as an embryological remnant; these cysts are observed in 0.5% to 7.9% of patients.<sup>1,2</sup> However, these improved imaging techniques have increased the incidental determination of midline prostatic cysts (MPCs) in adult males, and the frequency of these findings is currently estimated to be 5-14%.<sup>3</sup>

Although the majority of the patients are symptom-free, enlarged prostatic cysts can compress adjacent structures, such as the posterior urethra, bladder neck or seminal vesicles, and then the patients may suffer obstructive or irritative voiding symptoms, recurrent urinary tract infections, epididymitis, chronic pelvic pain syndrome, hematospermia, low semen volume, or even infertility.<sup>2-4</sup> Prostatic retention cysts rarely become symptomatic, but they may cause symptoms when the cyst enlarges to more than 3 cm. However, symptoms may occur even with smaller cysts if the location is just beside the bladder neck, and such cases are often misdiagnosed or confused with benign prostatic hyperplasia (BPH) or neuropathic bladder.<sup>2-5</sup>

We report on the case of a severely symptomatic, anteriorly located prostatic cyst arising from the bladder neck in a 30-year-old man who presented with lower urinary tract symptoms (LUTS), without any clinical evidence of benign prostatic hyperplasia or any endoscopic management. To our knowledge, symptomatic MPCs are generally located posteriorly and are rare. In fact, there are seven published reports of anteriorly positioned symptomatic MPCs arising from and obstructing the bladder neck with a ball-valve action during voiding.<sup>6-12</sup>

## CASE REPORT

A 30-year-old healthy man came to our outpatient clinic with a two-year history of severe LUTS, including frequent voiding, hesitancy, weak urinary stream and the sensation of residual urine. Despite alpha blocker drug treatment, his symptoms had worsened. His medical history was not significant in terms of previous urethral catheterization, urinary tract infection, pelvic/perineal trauma or neurological deficit. He had two children and did not have any ejaculatory complaints or infertility.

His International Prostate Symptom Score (IPSS) was 20, and his quality-of-life (QoL) score was 5. Digital rectal examination revealed a normal firm and nontender prostate

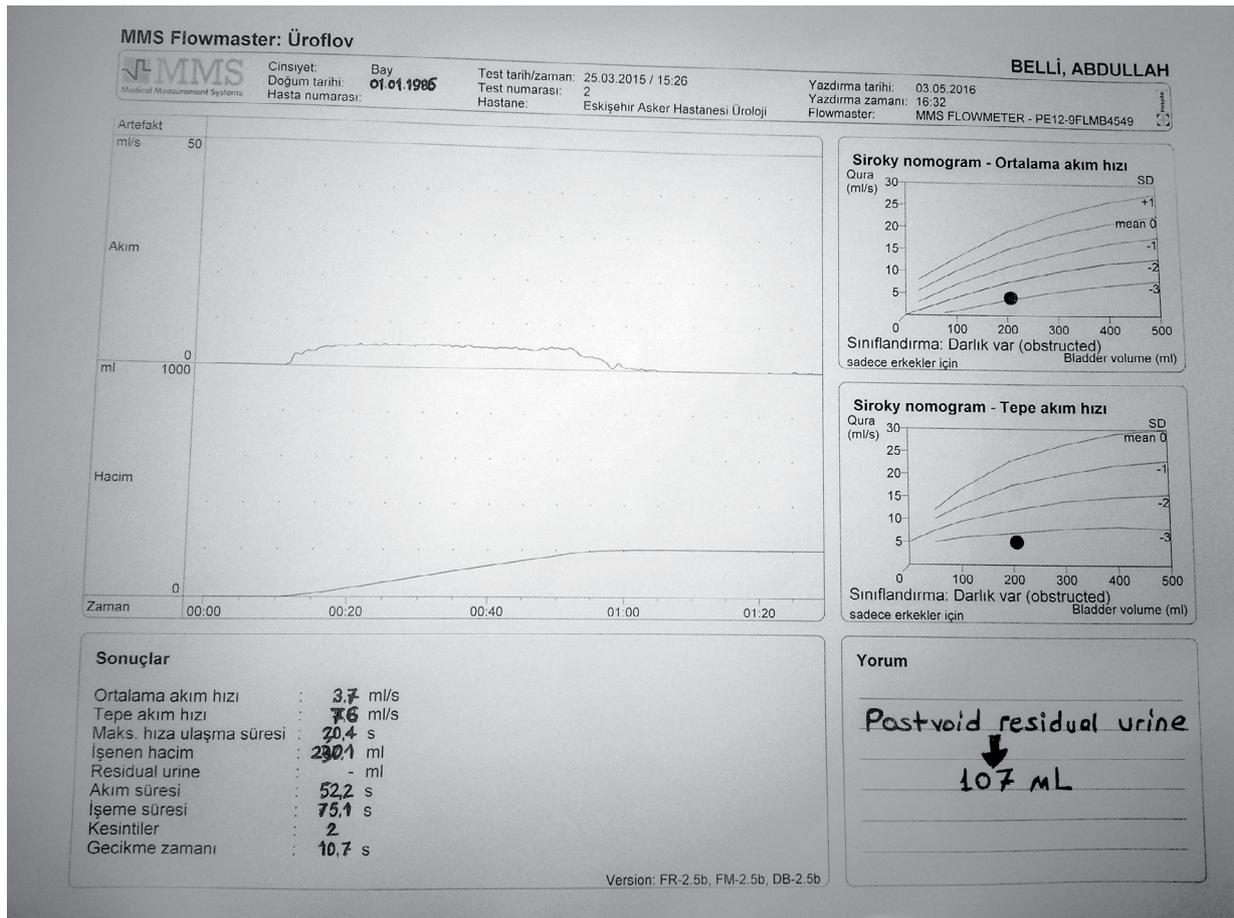
without palpable nodules. A routine urine examination was normal and the culture was sterile. The urine cytology was not suggestive of malignancy, the serum prostatic specific antigen (PSA) level was 0.82 ng/ml (the reference value for PSA for the age range of 30-40 years is 0-2 ng/ml), and routine biochemical laboratory examinations were within normal limits. Uroflowmetry (Figure 1) demonstrated a peak flow rate (Qmax) of 7.6 ml/sec with a voided volume of 230 ml, and the postvoid residual urine volume was 107 ml (the reference values are voided volume > 150 ml and Qmax >15 ml/s). TRUS showed an anteriorly positioned prostatic cyst arising from the bladder neck and obstructing the bladder outlet. The cyst diameter was approximately 13 x 10 mm, inside a prostate with a volume of 22 ml. CT urography was performed to identify the origin of the cystic lesion and to rule out ectopic ureter or ureterocele (Figure 2).

The patient then underwent cystourethroscopy examination under general anesthesia. This showed that the posterior wall of the prostatic urethra was normal and that there was cystic hemispherical bulging based on the anterior portion of the prostate. The bulge was located on the bladder neck at precisely twelve o'clock and was entirely compressing the bladder outlet. It was acting like a ball-valve, without lateral lobe hyperplasia (Figure 3). Moderate trabeculation due to gross back pressure change was also noted in the bladder. Transurethral marsupialization of the prostatic cyst to release the anatomical obstruction was performed, and milky fluid was expelled during the unroofing procedure.

A urethral catheter was left in place for two days, and the patient was then discharged. Histopathological examination revealed that the cyst wall was lined with benign flattened prostatic glandular epithelium without any preneoplastic change, which was consistent with the diagnosis of a prostatic retention cyst. At a return visit in the third postoperative month, a subjective dramatic improvement in symptoms was noted. IPSS was 5 and QoL was 2 at three months after the operation. Uroflowmetry showed an increased Qmax (18 ml/sec with a voided volume of 300 ml) and no residual urine. Furthermore, the patient had no symptoms suggestive of erectile dysfunction or ejaculation disorders.

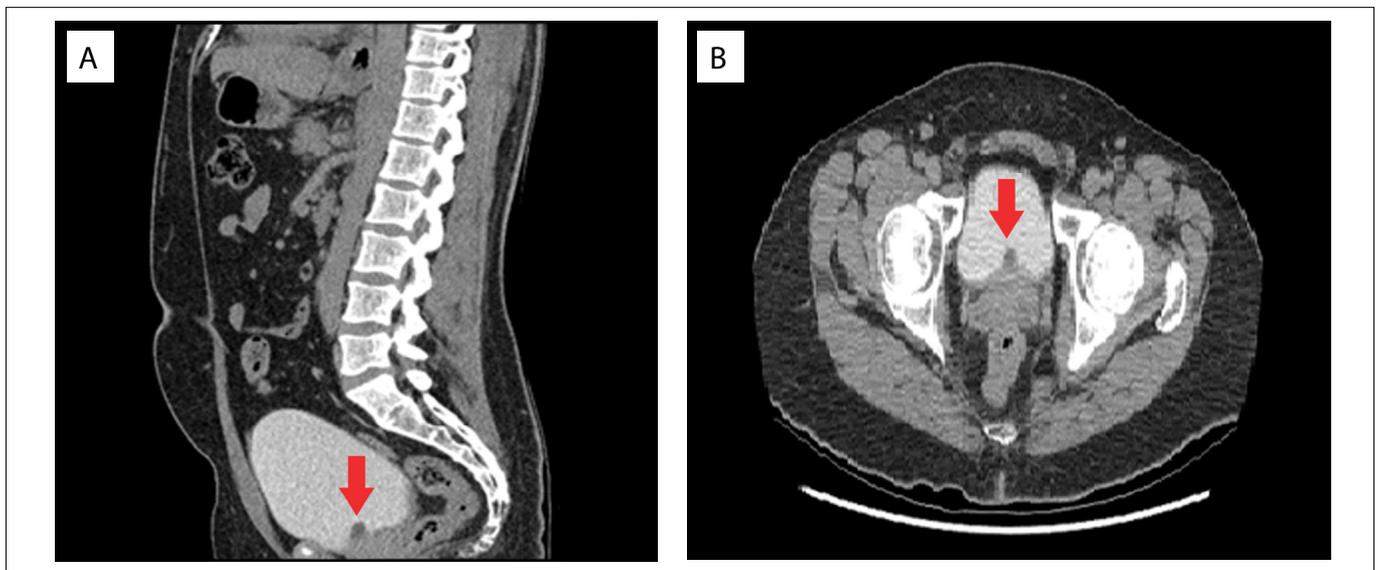
## DISCUSSION

Although lower male genitourinary tract cystic lesions are uncommon and usually benign, they may be associated with a variety of genitourinary abnormalities and symptoms, such as urinary tract infection, chronic pelvic pain syndrome, postvoiding incontinence, recurrent epididymitis, prostatitis, obstructive and/or irritative voiding symptoms, hematospermia, low semen volume, ejaculatory pain, or even infertility.<sup>2-4,9,13</sup>

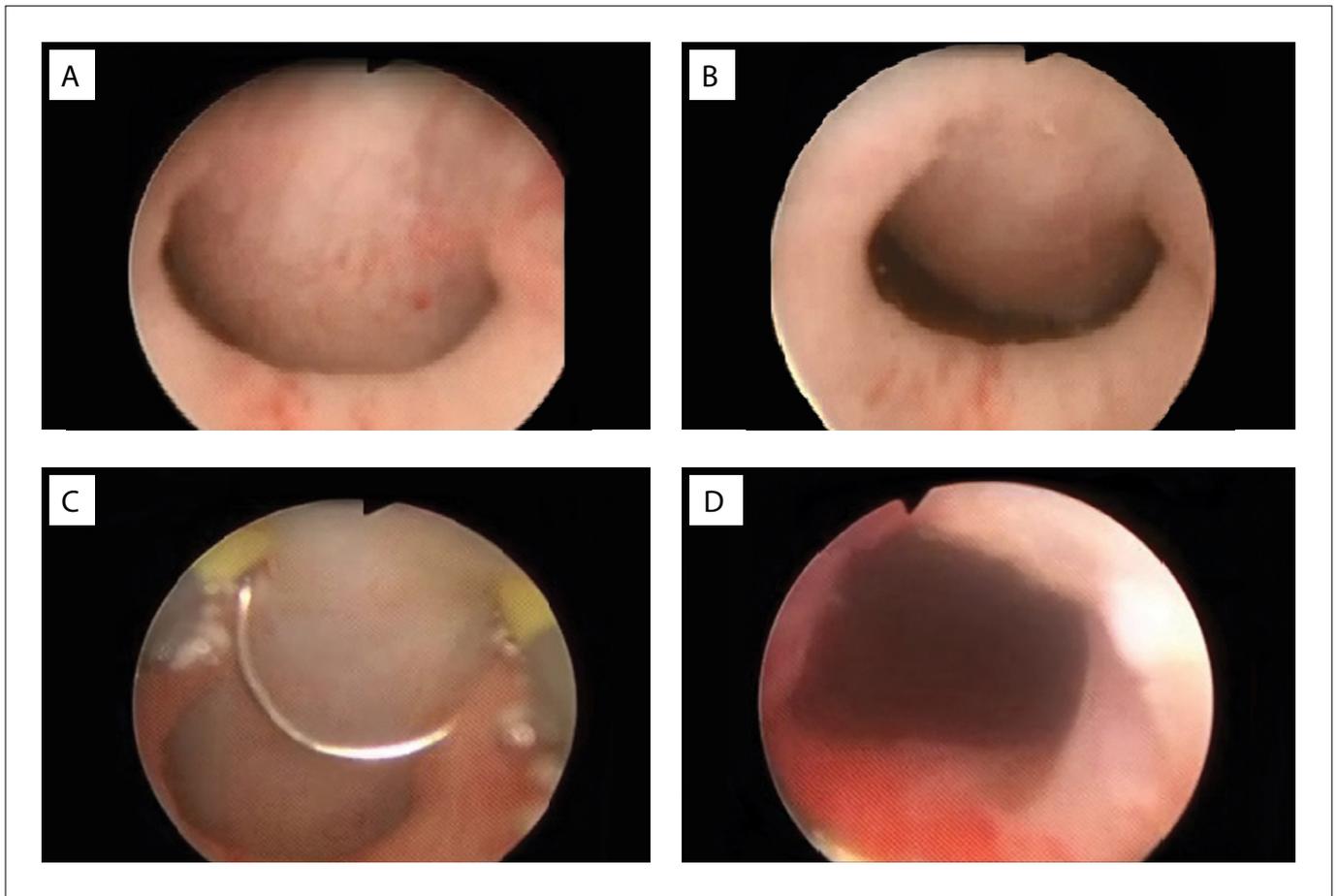


Uroflowmetry demonstrating average flow rate: 3.7 ml/sec; peak flow rate (Qmax): 7.6 ml/sec; time to reach maximum flow: 30.4 sec; voided volume: 230.1 ml; postvoid residual urine: 107 ml; flow time: 52.2 sec; voiding time: 75.1 sec; deductions: 2; delay time: 10.7 sec.

**Figure 1.** Preoperative uroflowmetry showing obstructed voiding.



**Figure 2.** Sagittal (A) and axial (B) computed tomography urography images showing low-density small nodular lesion in the bladder neck that represents the anteriorly positioned midline prostatic cyst (arrow).



**Figure 3.** (A) and (B): anteriorly positioned midline prostatic cyst obstructing the bladder neck with action like a ball-valve; (C) and (D): transurethral unroofing of the cyst.

Galosi et al. reported that MPCs are seen by TRUS in 9.8% of cases.<sup>1</sup> It has been reported that MPCs were observed in 7.6% of healthy men and 5% of symptomatic outpatients.<sup>2</sup> Over recent years, new imaging techniques such as TRUS, CT and MRI have increased the incidental determination of MPCs in adult males, and their frequency is currently estimated to be 5-14%.<sup>3,13,14</sup>

However, the majority of prostatic cysts are asymptomatic. They can be categorized as symptomatic when the cyst's presence is accompanied by infection or if its size and anatomical relationships affect the adjacent structures, which are most often located laterally.<sup>14</sup> An analysis on 34 patients with symptomatic prostatic cysts by Tambo et al.<sup>7</sup> revealed that 40% of the patients suffered from obstructive urinary symptoms, 33% from urinary retention, 9% from urodynia and 6% from infertility.

In 2009, Galosi et al.<sup>1</sup> classified prostatic cysts into six distinct types based on TRUS and pathological correlation: isolated medial cysts, cysts of the ejaculatory duct, simple or multiple parenchymal

cysts, complicated cysts (infectious or hemorrhagic), cystic tumors and secondary cysts relating to parasitic disease. MPCs are less common and are generally located posteriorly. They have traditionally been classified as Müllerian duct cysts and as enlarged prostatic utricles (mega-utricles), ejaculatory ducts, seminal vesicles and prostatic retention cysts.<sup>15,16</sup> Furuya et al.<sup>17</sup> classified MPCs, with or without the presence of sperm in the fluid content, using concomitant TRUS-guided opacification and dye injection. If there is communication with the seminal tract, then sperm can be found in the fluid content. They further classified MPCs into four categories: Type 1 MPC with no communication into the urethra (traditional prostatic utricle cyst); Type 2a MPC with no communication into the urethra [cystic dilatation of prostatic utricle (CDU)]; Type 2b CDU in communication with the seminal tract; and Type 3 cystic dilatation of the ejaculatory duct. They also found that the location, shape and volume of the MPC and the PSA level of the MPC fluid did not influence the classification.<sup>18</sup> This finding may be useful for classifying various kinds of midline cysts of the prostate. However, in practice, this classification is not used

**Table 1.** Search of the literature in medical databases for case reports on “Severe lower urinary tract symptoms due to anteriorly located midline prostatic cyst arising from the bladder neck in a young male”. The search was conducted on April 12, 2016

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	((Prostatic cyst[Title]) AND lower urinary tract symptoms[Title])	2	2
	((Prostatic cyst[Title]) AND midline[Title]) AND “case reports”[Publication Type]	3	1
	((Prostatic cyst[Title]) AND midline[Title])	7	2
Embase (via Elsevier)	((“Prostate”) or “Prostatic”) AND “Cysts” [Title Words] AND “case reports” [Publication Type]	0	0
LILACS (via Bireme)	((“Prostate”) or “Prostatic”) AND “Cysts” [Title Words] AND “case reports” [Publication Type]	2	0

because of the similarities of symptoms and primary treatment among prostate cysts.

According to the results from the pathological examination, our patient had a retention cyst of the prostate. This type of cyst is totally different from Müllerian duct cysts and prostatic utricle cysts, which are always lined with cuboidal or columnar epithelial cells. Retention cysts of the prostate gland are true acquired cysts and result from obstruction of prostatic glandular ductules, thus causing dilatation of the glandular acini. They can be located within any glandular zone of the prostate.<sup>16,17</sup> Moreover, there are no sperm cells in the fluid obtained from prostatic retention cysts, and they usually do not cause symptoms. However, on rare occasions, they may cause obstructive symptoms if located close to the bladder neck, as in the case of our patient.<sup>16,17</sup>

Although approximately 35 patients with symptomatic prostatic cysts have been reported, there are only seven published reports on anteriorly located MPCs.<sup>11</sup> Furthermore, to the best of our knowledge, only seven such cases of MPC of the bladder neck have been reported in the literature, as in our case. Also, this is the first case of an anteriorly located MPC of the bladder neck found in Turkey.<sup>7,11</sup>

Multiple therapeutic options have been described for management of symptomatic prostatic cysts, including transrectal aspiration with or without sclerotherapy, marsupialization with a transurethral technique and open surgery.<sup>7,18,19</sup> Although recurrences of cysts that were incompletely excised during open surgery have been reported, recurrence-free results have been reported for medial prostatic cysts treated with the transurethral technique.<sup>2,6</sup> Chang et al.<sup>10</sup> previously reported successful results from transurethral resection of an MPC presenting with LUTS. Zhang et al.<sup>20</sup> also recommended transurethral unroofing of small prostatic cysts (< 2 cm x 2 cm) that are close to the bladder cavity or urethra, because of the simplicity of the technique, the low risk of complications and the shorter convalescence period.

We searched for similar cases in different databases (PubMed, Embase and LILACS databases) using the terms: “prostatic cyst” AND “lower urinary tract symptoms” AND “midline” (Table 1). We found that few cases have been published.

Our patient was suffering from obstructive voiding problems rather than irritative symptoms, and transurethral unroofing of the prostatic cyst, which was located anteriorly in the midline position, provided satisfactory results for his complaints. In this case, standard transurethral resection of the prostate was avoided in order to prevent antegrade ejaculation and erectile dysfunction, in the absence of the lateral lobe of prostatic hyperplasia.

## CONCLUSION

Although symptomatic anteriorly located MPCs of the bladder neck, as described in the case presented here, are uncommon, they should be borne in mind in the differential diagnosis of obstructive voiding symptoms, especially in young patients and patients who do not respond to medical therapy such as use of alpha-blockers. Transurethral unroofing of the cyst may provide safe treatment with successful and satisfactory results in selected cases.

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# A rare association of intussusception and celiac disease in a child

## Associação rara entre intussuscepção e doença celíaca em criança

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### KEY WORDS:

Child.  
Intussusception.  
Celiac disease.  
Diarrhea.  
Gluten-free diet.

### PALAVRAS-CHAVE:

Criança.  
Intussuscepção.  
Doença celíaca.  
Diarreia.  
Dieta livre de glúten.

### ABSTRACT

**CONTEXT:** Intussusception is a common cause of acute intestinal obstruction in the pediatric population and it is normally idiopathic. Rare cases of chronic intussusception require investigation with greater attention.

**CASE REPORT:** We present a clinical case of a three-year-old boy with aqueous diarrhea, abdominal distension, vomiting and weight loss over a two-month period. During the investigation, abdominal ultrasound showed imaging of intussusception. The intraoperative findings showed the intussusception had resolved spontaneously. In further investigation, it was found that the diarrhea was malabsorptive and, after the patient underwent upper gastrointestinal endoscopy, a diagnosis of celiac disease was made. After a gluten-free diet was introduced, the patient showed complete remission of symptoms and regained weight, and normal growth was reestablished.

**CONCLUSION:** If the clinical presentation of intussusception is unusual, etiological investigation should be undertaken. In this case report, celiac disease was the underlying cause.

### RESUMO

**CONTEXTO:** Intussuscepção é uma causa frequente de obstrução intestinal aguda em pacientes pediátricos, e geralmente é idiopática. Raros casos de intussuscepção crônica devem ser investigados com maior atenção.

**RELATO DE CASO:** Apresentaremos um caso clínico de um menino de três anos com diarreia aquosa, distensão abdominal, vômito e perda de peso por dois meses, cuja investigação por ultrassonografia abdominal revelou imagem de intussuscepção. Os achados intraoperatórios mostraram que a intussuscepção havia se resolvido espontaneamente. Em investigação subsequente, foi identificado que a diarreia era malabsortiva e, após a realização de endoscopia digestiva alta, foi feito diagnóstico de doença celíaca. Foi iniciada dieta com restrição de glúten e o paciente teve remissão completa dos sintomas, recuperou peso e o crescimento foi restabelecido.

**CONCLUSÃO:** Caso a apresentação clínica de intussuscepção não seja a habitual, deve-se prosseguir a investigação etiológica. No caso clínico apresentado, doença celíaca foi a causa subjacente.

**INTRODUCTION**

Intussusception is a common cause of small bowel obstruction in children under five years of age, and its classical symptoms include acute abdominal pain, red currant jelly stools and abdominal mass. However, these classical symptoms are not always present and it sometimes mimics acute viral gastroenteritis, with diarrhea and vomiting. Invagination of the proximal bowel into the distal bowel results in venous congestion and bowel wall edema.<sup>1</sup> If not promptly diagnosed and treated, this condition can lead to arterial obstruction, bowel necrosis and perforation. Almost 90% of the etiology of intussusception in children is ileocolic and idiopathic.<sup>1</sup> The lead point of the invagination is lymphoid hyperplasia of the small bowel, but Meckel's diverticulum, polyps and trauma can also lead to this problem. Intussusception is diagnosed by means of abdominal ultrasound and can be treated surgically or non-surgically.

This case report describes the presence of intussusception in a child with a chronic history of diarrhea, which is an unusual presentation in children that should indicate the possibility of a different diagnosis. After the case description, there is a brief discussion with a systematic search of data in the PubMed, Cochrane and LILACS databases (Table 1).

**CASE REPORT**

A three-year-old boy with a history of liquid diarrhea for a couple of days, several times a day, with intermittent vomiting and without blood on stools or fever, was first seen by a primary care physician. At physical examination, the child was found to be hydrated, without abdominal pain or distention, and was able to take oral fluids and medication. He was diagnosed as having acute gastroenteritis and was advised to take oral hydrate solution and to return to the primary care center if the symptoms worsened. Fourteen days later, the child returned and the mother complained that he had been suffering from intermittent diarrhea, vomiting and abdominal distention. At examination, he did not show any weight loss, was hydrated and had an overall good clinical condition. At this point, the diagnosis was persistent diarrhea and he was advised to start a lactose-free

diet, take albendazole for five days and collect parasitological stool samples.

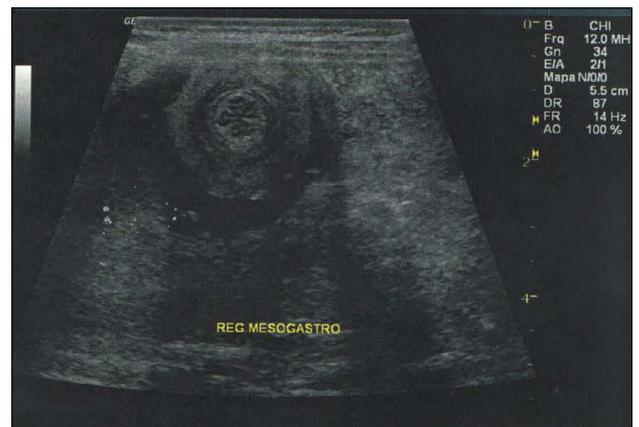
There was no short-term follow-up on this case by the primary care team because the family requested a second opinion from a different general pediatrician. The second physician made the interpretation that the child possibly had lactose intolerance and ordered a lactose intolerance test with blood analysis. When the patient returned to the original primary care center, two months after the initial onset, he was still presenting aqueous diarrhea three to six times a day, abdominal distension, intermittent vomiting and now weight loss. Parasitological stool samples were negative and blood analysis suggested an iron deficient anemia. The lactose intolerance test was not available at that moment. The diagnosis at this point was chronic diarrhea with probable malabsorption. The child was referred to a tertiary gastroenterology center for further investigation, with upper gastrointestinal endoscopy, serum xylose tests and stool analysis for fat and pH.

Abdominal ultrasound was performed and identified an onionskin image of part of the small bowel (Figure 1), suggestive of intussusception. On the day of the ultrasound, the patient presented a distended but soft palpable abdomen without abdominal pain and was referred for hospital admission. After hospital admission, laparoscopic intervention demonstrated dilation of the proximal small bowel, without any mass or enlarged lymph nodes.

The intraoperative findings showed that the intussusception had resolved spontaneously. During the hospital stay, further investigations on chronic diarrhea and malabsorption were conducted, and the most relevant results were the following: low albumin of 3.2 g/dl; increased international normalized ratio (INR) of 1.95, which resolved after vitamin K administration; low serum sodium (Na) of 133 mEq/l; high presence of fat in stools (12 g of fat in 161.7 g of stool after 72 hours) and normal stool pH of 6.0; low serum xylose of 6.08 mg/dl, suggestive

**Table 1.** Database search results for the relationship between intussusception and celiac disease and child. Search performed on February 22, 2016

Database	Search strategy (descriptors)	Articles found	Articles included
MEDLINE (PubMed)	(Intussusception) AND (Celiac disease) AND (child)	24	4
	(Intussusception) AND (child)	2633	1
	(Intussusception) AND (Celiac disease)	0	0
LILACS	(Intussusception) AND (Celiac disease)	6	0



**Figure 1.** Abdominal ultrasound image showing an onionskin-like part of the small bowel suggestive of intussusception.

of malabsorption; negative HIV serological test; normal immunoglobulin A (IgA) antibody level of 247 mg/dl; and normal sweat test (Na of 44.01 mEq/l and Cl of 35.6 mEq/l). All of these laboratory and reference values are shown in Table 2. To investigate malabsorption, upper gastrointestinal endoscopy was performed, and macroscopic evaluation showed a mosaic pattern of mucosa suggestive of celiac disease. On microscopic evaluation, inflammation of the duodenum mucosa was observed along with atrophic intestinal villi and crypt hypertrophy, compatible with Marsh III celiac disease, which was further confirmed by elevated tissue transglutaminase antibody concentration of 200 U/ml.

The child was then administered a gluten-free diet and his weight, stool consistency and stool frequency recovered completely, thus resolving the abdominal distention. He was discharged after a month in hospital, with body weight of 16.1 kg. One month later, at an outpatient visit, he was weighing 17.4 kg. One year after admission, his weight had increased to 19.8 kg.

## DISCUSSION

Idiopathic intussusception is a common cause of small bowel obstruction in children between the ages of 3 months and 5 years and has been recently correlated with underlying celiac disease.<sup>1-4</sup> It is the most common cause of intestinal obstruction at pediatric ages and needs prompt intervention, which may be surgical or nonsurgical.

Non-operative methods for treating intussusception include barium enema and hydrostatic or pneumatic reduction. While non-operative methods are used more commonly than surgical intervention, the latter may still be needed when there are complications (peritonitis, perforation or profound shock) or when non-operative intervention is unsuccessful, or in situations of lack of a trained professional for non-invasive approaches.<sup>1</sup>

**Table 2.** Patient's laboratory result values and reference values for normality

	Patient's values	Reference values
Albumin (g/dl)	3.2	3.8-5.4
International normalized ratio (INR)	1.95	1-1.2
Sodium (Na) (mEq/l)	133	136-145
Stool weight (g/day)	161.7	< 160 (< 1% of body weight)
Fat in stool (g/day)	12	< 2
pH in stool	6.0	5.0-7.0
Serum xylose (mg/dl)	6.08	> 20
IgA antibody (mg/dl)	247	33-308
Sweat test Na (mEq/l)	44.01	< 50
Sweat test Cl (mEq/l)	35.6	< 60
Tissue transglutaminase antibody (U/ml)	200	< 10

IgA = immunoglobulin A.

Most cases of intestinal intussusception at pediatric ages are idiopathic, and the lead point is generally lymphoid hyperplasia of the small bowel. The classical symptoms of intussusception include acute abdominal pain, red currant jelly stools and abdominal mass in a child with normal nutritional status. If the child fails to thrive and has chronic diarrhea, pain or blood stools, further investigation should be conducted after treating the intussusception, as was done in our patient. The differential diagnoses include Meckel's diverticulum, polyps, trauma, celiac disease and enteropathy-associated T-cell lymphoma, among others.<sup>1</sup>

Celiac disease is a chronic inflammatory intestinal disease that occurs in about 1 to 2% of the general population. Untreated celiac disease has therefore been correlated with intussusception, and this association has been documented by a number of case reports.<sup>2-4</sup> The proposed cause of intussusception in cases of celiac disease is diffuse inflammation and thickening of the intestinal wall, which lead to hyperperistalsis and increased dilation of the small bowel. This, in turn, could be the lead point for intussusception, which can develop singly or multiply, chronically and with self-resolution or the need for surgical intervention. Less frequently, but with worse prognosis, this lead point could also be associated with a focal lead point in lymphomas.<sup>4</sup>

The majority of studies on this subject are case descriptions or series of cases, and there is a lack of case-control or randomized clinical studies. In a recent retrospective study on patients undergoing imaging for abdominal pain, intussusception was found more frequently in patients with untreated celiac disease (less than nine months before celiac disease was diagnosed) than in the general population (1.2% versus 0.07% respectively).<sup>2</sup> In a large case-control study evaluating the risk of late celiac disease in patients with intussusception, no significant association was found.<sup>3</sup> Nonetheless, using a prospective cohort approach, a post-hoc analysis found that 12 out of 29,060 individuals with celiac disease were given a diagnosis of intussusception after the onset of celiac disease, with a modest but significant increase risk of intussusception after celiac disease had been diagnosed (odds ratio, OR = 1.95; 95% confidence interval, CI = 1.01-3.77; P = 0.046). In that study, patients with celiac disease without symptoms were not serially investigated with abdominal imaging, which may have reduced the absolute numbers of patients with subclinical intussusception who did not seek acute care and were unaccounted for.

Because intussusception in celiac patients may be chronic and painless, it is probably underdiagnosed. Patients with celiac disease may undergo imaging for chronic abdominal pain and intussusception may be identified by chance, as it is usually not the first differential diagnosis in these cases. While in adults most cases of intussusception are investigated because it is always a pathological condition, in children this is only done when an

abnormal clinical presentation or physical examination ensues, since it is considered to be a common cause of idiopathic intestinal obstruction.

What makes our case description original is the chronic presentation of intussusception with spontaneous resolution, without the need for surgical intervention. This finding has only infrequently been described. The majority of case descriptions found in the literature describe an emergency situation of intussusception, in a child who failed to thrive.<sup>4,5</sup> It will only be determined whether spontaneous resolution in these situations is more frequent when routine abdominal ultrasound becomes part of the celiac disease protocol workup. A large serial study on pediatric populations with celiac disease with routine abdominal ultrasound might help in resolving this question.

## CONCLUSION

Intussusception is a common cause of idiopathic acute intestinal obstruction in children. If the clinical presentation is unusual, this may prompt further investigation. In this case, celiac disease was the pathological condition behind the findings, with clinical presentation of chronic painless intussusception, without any need for surgical intervention and with signs and symptoms of malabsorption.

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# Gamma-glutamyl transferase and pulmonary embolism

## Gama glutamil transferase e embolia pulmonar

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Dear Editor,

We read the article “Elevated gamma glutamyl transferase (GGT) levels are associated with the location of acute pulmonary embolism. Cross-sectional evaluation in hospital setting” by Korkmaz et al.<sup>1</sup> They concluded that there was a significant association between increased embolism load in the pulmonary artery and increased serum GGT levels.

Several noninvasive tests have been used for accurately diagnosing pulmonary embolism. Some inflammatory markers like red cell distribution width may show pulmonary embolism through further diagnostic tests.<sup>2</sup> In addition, mean platelet volume may describe or predict pulmonary embolism.<sup>3</sup> Tests for these markers are routine, available and accessible through any laboratory. Serum GGT activity is a marker of oxidative stress and endothelial dysfunction. We previously showed that serum GGT level may be an independent marker for the severity of cardiovascular diseases.<sup>4</sup> Korkmaz et al.<sup>1</sup> showed the correlation between GGT and acute pulmonary embolism. However, some important issues need to be considered. Firstly, GGT determination is one of the hepatic function tests. Presence of GGT may change any form of hepatic dysfunction even if no overt liver disease is present. Secondly, Gilbert syndrome is frequently seen worldwide. This syndrome may be correlated with hepatic function tests. GGT is also a widely measured serum enzyme: it almost specifically shows biliary epithelial damage and generally indicates excessive alcohol intake. GGT is released from many tissues such as the liver, kidney, cerebrovascular endothelium and pericytes.<sup>5</sup> Furthermore, changes in serum GGT levels can be affected by waist circumference and body mass index, hypertension, diabetes, hyperuricemia and genetic factors. Lastly, admission troponin levels were assessed in the recent study by Korkmaz et al.,<sup>1</sup> but the patients seemed to have a relatively long duration of symptoms before admission, which may have led to underestimation of the potential impact of troponin.

In conclusion, although GGT levels were associated with pulmonary embolism in the study published in this journal,<sup>1</sup> GGT levels alone may not provide enough information to diagnose these patients, unless the factors outlined above are also taken into consideration. Therefore, we believe that GGT should be evaluated under these conditions. We believe that these findings will be clarified through further studies.

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# Screening for chronic kidney disease and inequity

## Rastreamento de doença renal crônica e iniquidade

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### To the Editor,

The editorial about screening for chronic kidney disease (CKD) is quite interesting<sup>1</sup> and gives us a good grasp of the epidemiological burden of this disease and various aspects of its morbidity and mortality, as well as many insights about the complex relations between disease and socioeconomic status. However, the conclusion that screening could potentially reduce inequity in the Brazilian population, based on correlating CKD with socioeconomic status, is flawed.

There is plenty of evidence showing that most screening tends to produce more inequity, rather than reducing it. This is particularly so if it is done in countries where the public health system is insufficiently organized and not strong enough to be regulated in its entirety and/or if screening programs are not publicly organized, thereby leading to so-called “opportunistic screening”.<sup>2</sup> This is almost always the case in places with an uncoordinated health system and a strong private health sector.

For instance, if screening for CKD were to be started in Brazil, it is certain that within a short period of time, thousands of wealthy low-risk people would undergo this screening and, most probably, the poor low-educated high-risk population would not have the same access to it as enjoyed by the first group.<sup>3</sup> Apart from this worrisome increase in inequity, introduction of a new screening intervention would also, potentially and paradoxically, increase the degree of harm among those undergoing opportunistic screening precisely because they would be low-risk individuals. Consequently, screening would have less benefit and there would be a higher degree of overdiagnosis.

Screening is a complex issue with many unsuspected variables playing an important role in the outcomes. Furthermore, a screening program would have to go through the rigorous control of a well-designed randomized controlled trial showing its effectiveness before it is put into practice.

Lastly, the best thing to do towards reducing healthcare inequity, in terms of healthcare policy, is to promote a universal coordinated public healthcare system,<sup>4</sup> strongly based on primary care and without great interference from the private sector. Outside of such a system, promotion of any intervention will inexorably lead to more inequity.

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# Chemotherapy for advanced non-small cell lung cancer in the elderly population

This is the abstract of a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews 2015, issue 10, art. no. CD010463. DOI: 10.1002/14651858.CD010463.pub2. For full text and details about the authors, see reference 1.

Fábio Nasser Santos, Tiago Biachi de Castría,  
Marcelo Rocha Souza Cruz, Rachel Riera

*The independent commentary was written by Célia Tosello de Oliveira*

## ABSTRACT

**BACKGROUND:** Approximately 50% of patients with newly diagnosed non-small cell lung cancer (NSCLC) are over 70 years of age at diagnosis. Despite this fact, these patients are underrepresented in randomized controlled trials (RCTs). As a consequence, the most appropriate regimens for these patients are controversial, and the role of single-agent or combination therapy is unclear. In this setting, a critical systematic review of RCTs in this group of patients is warranted.

**OBJECTIVES:** To assess the effectiveness and safety of different cytotoxic chemotherapy regimens for previously untreated elderly patients with advanced (stage IIIB and IV) NSCLC. To also assess the impact of cytotoxic chemotherapy on quality of life.

### METHODS:

*Search methods:* We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 10), MEDLINE (1966 to 31 October 2014), EMBASE (1974 to 31 October 2014), and Latin American Caribbean Health Sciences Literature (LILACS) (1982 to 31 October 2014). In addition, we handsearched the proceedings of major conferences, reference lists from relevant resources, and the ClinicalTrial.gov database.

*Selection criteria:* We included only RCTs that compared non-platinum single-agent therapy versus non-platinum combination therapy, or non-platinum therapy versus platinum combination therapy in patients over 70 years of age with advanced NSCLC. We allowed inclusion of RCTs specifically designed for the elderly population and those designed for elderly subgroup analyses.

*Data collection and analysis:* Two review authors independently assessed search results, and a third review author resolved disagreements. We analyzed the following endpoints: overall survival (OS), one-year survival rate (1yOS), progression-free survival (PFS), objective response rate (ORR), major adverse events, and quality of life (QoL).

**MAIN RESULTS:** We included 51 trials in the review: non-platinum single-agent therapy versus non-platinum combination therapy (seven trials) and non-platinum combination therapy versus platinum combination therapy (44 trials).

## Non-platinum single-agent versus non-platinum combination therapy

Low-quality evidence suggests that these treatments have similar effects on overall survival (hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.72 to 1.17; participants = 1062; five RCTs), 1yOS (risk ratio (RR) 0.88, 95% CI 0.73 to 1.07; participants = 992; four RCTs), and PFS (HR 0.94, 95% CI 0.83 to 1.07; participants = 942; four RCTs). Non-platinum combina-

tion therapy may better improve ORR compared with non-platinum single-agent therapy (RR 1.79, 95% CI 1.41 to 2.26; participants = 1014; five RCTs; low-quality evidence).

Differences in effects on major adverse events between treatment groups were as follows: anemia: RR 1.10, 95% CI 0.53 to 2.31; participants = 983; four RCTs; very low-quality evidence; neutropenia: RR 1.26, 95% CI 0.96 to 1.65; participants = 983; four RCTs; low-quality evidence; and thrombocytopenia: RR 1.45, 95% CI 0.73 to 2.89; participants = 914; three RCTs; very low-quality evidence. Only two RCTs assessed quality of life; however, we were unable to perform a meta-analysis because of the paucity of available data.

## Non-platinum therapy versus platinum combination therapy

Platinum combination therapy probably improves OS (HR 0.76, 95% CI 0.69 to 0.85; participants = 1705; 13 RCTs; moderate-quality evidence), 1yOS (RR 0.89, 95% CI 0.82 to 0.96; participants = 813; 13 RCTs; moderate-quality evidence), and ORR (RR 1.57, 95% CI 1.32 to 1.85; participants = 1432; 11 RCTs; moderate-quality evidence) compared with non-platinum therapies. Platinum combination therapy may also improve PFS, although our confidence in this finding is limited because the quality of evidence was low (HR 0.76, 95% CI 0.61 to 0.93; participants = 1273; nine RCTs).

Effects on major adverse events between treatment groups were as follows: anemia: RR 2.53, 95% CI 1.70 to 3.76; participants = 1437; 11 RCTs; low-quality evidence; thrombocytopenia: RR 3.59, 95% CI 2.22 to 5.82; participants = 1260; nine RCTs; low-quality evidence; fatigue: RR 1.56, 95% CI 1.02 to 2.38; participants = 1150; seven RCTs; emesis: RR 3.64, 95% CI 1.82 to 7.29; participants = 1193; eight RCTs; and peripheral neuropathy: RR 7.02, 95% CI 2.42 to 20.41; participants = 776; five RCTs; low-quality evidence. Only five RCTs assessed QoL; however, we were unable to perform a meta-analysis because of the paucity of available data.

**AUTHORS' CONCLUSIONS:** In people over the age of 70 with advanced NSCLC who do not have significant co-morbidities, increased survival with platinum combination therapy needs to be balanced against higher risk of major adverse events when compared with non-platinum therapy. For people who are not suitable candidates for platinum treatment, we have found low-quality evidence suggesting that non-platinum combination and single-agent therapy regimens have similar effects on survival. We are uncertain as to the comparability of their adverse event profiles. Additional evidence on quality of life gathered from additional studies is needed to help inform decision making.

The abstract, the full text of this review (English) and a plain language summary (for patients and consumers, in English, Croatian, German and Russian) are available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010463.pub2/full>

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1. Santos FN, de Castría TB, Cruz MR, Riera R. Chemotherapy for advanced non-small cell lung cancer in the elderly population. Cochrane Database Syst Rev. 2015;(10):CD010463.

## COMMENTS

There is still no consensus in the literature regarding the benefit of chemotherapy for advanced non-small cell lung cancer in the elderly population over 70 years of age, with regard to overall survival, one-year survival rate, progression-free survival, objective response rate, major adverse events and quality of life.

This review article based on randomized controlled trials showed that among patients without significant comorbidities, platinum combination therapy led to longer survival than seen with non-platinum therapy, provided that the risk of side effects is addressed. However, patients who are not suitable candidates for platinum treatment do not benefit from combination therapy, in comparison with single-agent therapy regimens, and develop similar side effects.

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# Anabolic steroids for rehabilitation after hip fracture in older people

This is the abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews (CDSR) 2014, issue 10. art. no.: CD008887. DOI: 10.1002/14651858.CD008887.pub2

Vaqas Farooqi, Maayken E. L. van den Berg, Ian D. Cameron, Maria Crotty

*The independent commentary was written by Mauricio de Miranda Ventura*

## ABSTRACT

**BACKGROUND:** Hip fracture occurs predominantly in older people, many of whom are frail and undernourished. After hip fracture surgery and rehabilitation, most patients experience a decline in mobility and function. Anabolic steroids, the synthetic derivatives of the male hormone testosterone, have been used in combination with exercise to improve muscle mass and strength in athletes. They may have similar effects in older people who are recovering from hip fracture.

**OBJECTIVES:** To examine the effects (primarily in terms of functional outcome and adverse events) of anabolic steroids after surgical treatment of hip fracture in older people.

### METHODS:

*Search methods:* We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialized Register (10 September 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2013 Issue 8), MEDLINE (1946 to August Week 4 2013), EMBASE (1974 to 2013 Week 36), trial registers, conference proceedings, and reference lists of relevant articles. The search was run in September 2013.

*Selection criteria:* Randomized controlled trials of anabolic steroids given after hip fracture surgery, in inpatient or outpatient settings, to improve physical functioning in older patients with hip fracture.

*Data collection and analysis:* Two review authors independently selected trials (based on predefined inclusion criteria), extracted data and assessed each study's risk of bias. A third review author moderated disagreements. Only very limited pooling of data was possible. The primary outcomes were function (for example, independence in mobility and activities of daily living) and adverse events, including mortality.

**MAIN RESULTS:** We screened 1290 records and found only three trials involving 154 female participants, all of whom were aged above 65 years and had had hip fracture surgery. All studies had methodological shortcomings that placed them at high or unclear risk of bias. Because of this high risk of bias, imprecise results and likelihood of publication bias, we judged the quality of the evidence for all primary outcomes to be very low.

These trials tested two comparisons. One trial had three groups and contributed data to both comparisons. None of the trials reported on patient acceptability of the intervention.

Two very different trials compared anabolic steroid versus control (no anabolic steroid or placebo). One trial compared anabolic steroid injections (given weekly until discharge from hospital or four weeks, whichever came first) versus placebo injections in 29 "frail elderly females". This found very low quality evidence of little difference between the two groups in the numbers discharged to a higher level of care or dead (one person in the control group died) (8/15 versus 10/14; risk ratio

(RR) 0.75, 95% confidence interval (CI) 0.42 to 1.33;  $P = 0.32$ ), time to independent mobilization or individual adverse events. The second trial compared anabolic steroid injections (every three weeks for six months) and daily protein supplementation versus daily protein supplementation alone in 40 "lean elderly women" who were followed up for one year after surgery. This trial provided very low quality evidence that anabolic steroid may result in less dependency, assessed in terms of being either dependent in at least two functions or dead (one person in the control group died) at six and 12 months, but the result was also compatible with no difference or an increase in dependency (dependent in at least two levels of function or dead at 12 months: 1/17 versus 5/19; RR 0.22, 95% CI 0.03 to 1.73;  $P = 0.15$ ). The trial found no evidence of between-group differences in individual adverse events.

Two trials compared anabolic steroids combined with another nutritional intervention ('steroid plus') versus control (no 'steroid plus'). One trial compared anabolic steroid injections every three weeks for 12 months in combination with daily supplement of vitamin D and calcium versus calcium only in 63 women who were living independently at home. The other trial compared anabolic steroid injections every three weeks for six months and daily protein supplementation versus control in 40 "lean elderly women". Both trials found some evidence of better function in the steroid plus group. One trial reported greater independence, higher Harris hip scores and gait speeds in the steroid plus group at 12 months. The second trial found fewer participants in the anabolic steroid group were either dependent in at least two functions, including bathing, or dead at six and 12 months (one person in the control group died) (1/17 versus 7/18; RR 0.15, 95% CI 0.02 to 1.10;  $P = 0.06$ ). Pooled mortality data (2/51 versus 3/51) from the two trials showed no evidence of a difference between the two groups at one year. Similarly, there was no evidence of between-group differences in individual adverse events. Three participants in the steroid group of one trial reported side effects of hoarseness and increased facial hair. The other trial reported better quality of life in the steroid plus group.

**AUTHORS' CONCLUSIONS:** The available evidence is insufficient to draw conclusions on the effects, primarily in terms of functional outcome and adverse events, of anabolic steroids, either separately or in combination with nutritional supplements, after surgical treatment of hip fracture in older people. Given that the available data points to the potential for more promising outcomes with a combined anabolic steroid and nutritional supplement intervention, we suggest that future research should focus on evaluating this combination.

The full-text of this review (English), the abstract (English and French) and a plain language summary (for patients and consumers, in English and French) are available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008887.pub2/full>

## REFERENCE

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## COMMENTS

Sarcopenia is a trademark of aging that consists of progressive loss of muscle mass. When this is accompanied by functional impairment, thus compromising elderly people's independence and autonomy, the condition is known as frailty syndrome. This condition leads to decreased activity, mobility and bone mass and a predisposition towards falls, another

geriatric syndrome of great importance. Both frailty syndrome and fall syndrome bring in their wake increased morbidity, mortality and compromised independence and autonomy among elderly people.

It might be thought that, after surgery on an elderly individual to correct a femoral fracture resulting from a fall, use of steroids alone for rehabilitation may be beneficial towards recovering the individual's mobility, independence and autonomy. However, this would ignore the whole process and physiopathological condition that led to this event.

Fundamentally, the history of patients who have fallen needs to be known. Were they previously independent and autonomous? Do they have any chronic degenerative disease (hypertension, diabetes mellitus, heart failure or stroke sequelae)? What were their cognition levels prior to the fall (did they present dementia?)? Within this age group, patients have widely varying states of functionality, which is well known to interfere with making prognoses.

One important issue in evaluating elderly individuals' recovery concerns their functionality, particularly in comparison with their previous condition. The main objective of any procedure and treatment for patients in this age group is to maintain their independence and autonomy.

In analyzing sarcopenia in elderly people, coupled with frailty and fall syndromes, this process needs to be understood as part of a set of factors. Malnutrition *per se* does not have as important a role in relation to the prevalence of sarcopenia as low protein intake does. Other factors involved include physical inactivity (which accentuates the loss of muscle mass), neuroendocrine deregulation (for which the most classic examples are glucose intolerance and hypothyroidism) and immune dysfunction (for example, increased levels of interleukins 1 and 6, and of tumor necrosis factor, and decreased cellular immunity). Given this complexity of events that culminate in sarcopenia among elderly people, decreased testosterone levels in these patients are only rarely seen. It has already been shown that hormone supplementation does not meet the expectations for improvement of muscle mass and functional performance, especially when this is done alone, without taking the other factors into consideration. It is unsurprising that when physical activity is added to administration of steroids, the results tend to be a little better. However, these results are not so significantly better as to justify use of steroids.

There have not been any reports of improved muscle strength in frail elderly individuals through calcium replacement. Until not long ago, it was believed that vitamin D replacement at high doses could reduce the loss of muscle strength, thus reducing the risk of falls and fractures. However, even this has been questioned recently.

Lastly, the issue of tolerability was undervalued in these studies, given that diseases strongly associated with steroid replacement, such as atherosclerotic vascular diseases and neoplastic diseases (liver, testes and prostate), were not even mentioned. The short durations of these studies will clearly have interfered with such associations, but some kind of assessment in this regard, so as to ensure that the therapy was tolerable, should have been conducted.

Therefore, it is not surprising that the results from this systematic review do not recommend steroid replacement for improving muscle strength in elderly individuals subsequent to operative femoral fracture repair. The reality of frail elderly individuals who fall is much more complex than this.

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Grants, bursaries and any other financial support for studies must be mentioned separately after the references, in a section named "Acknowledgements", along with any other acknowledgements to individuals or professionals who have helped in producing the study but whose contribution does not constitute authorship (we recommend that the item "Authorship" at <http://www.icmje.org> should be read to obtain clarifications regarding the criteria for authorship).

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#### References

The list of references (in the "Vancouver style", as indicated by the International Committee of Medical Journal Editors, ICMJE) should be laid out in the final part of the article, after the conclusions and before the tables and figures. In the text, the references must be numbered according to the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences (see examples in the preceding section), and must be in superscript form (without using parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references cited in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into their computer internet browsers, the journal's readers will be taken to the exact document cited, and not to a general website. The following are some examples of the most common types of references:

##### Article in journal

- Hurt AC, Hardie K, Wilson NJ, et al. Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. *N Engl J Med*. 2011;365(26):2541-2.

##### Chapter of book

- Miller WI, Achernabb JC, Fluck CE. The adrenal cortex and its disorder. In: Sperling M. *Pediatric endocrinology*. 3<sup>rd</sup> ed. Elsevier Health Sciences; 2008. p. 444-511.

##### Text on the internet

- Centers for Disease Control and Prevention. Children's food environment State Indicator Report, 2011. Available from: <http://www.cdc.gov/obesity/downloads/ChildrensFoodEnvironment.pdf>. Accessed in 2012 (Mar 7).

#### Figures and tables

Images must have good resolution (minimum of 300 DPI) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint documents. If photographs are inserted in a

Microsoft Word file, the images should also be sent separately. Graphs must be prepared in Microsoft Excel (do not send them in image formats) and must be accompanied by the tables of data from which they have been generated. The number of illustrations must not exceed the total number of pages minus one.

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The legend or title sentence should be short but comprehensible without depending on reading the article.

All the figures and tables should be cited in the text.

São Paulo Medical Journal/Evidence for Health Care is for now published in black-and-white in its printed version. Photographs, photomicrographs, bar and line graphs and any image to be published must be prepared considering that there will be no color differentiation (any color information will be discarded). Shades of gray and printing patterns (dots, stripes and others) should be used instead, with good contrast.

#### Original articles

Clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies, and systematic reviews with or without meta-analysis, are considered to be original articles.

The São Paulo Medical Journal/Evidence for Health Care 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, from 2008 onwards, manuscripts on clinical trials have been accepted for publication only if they have received an identification number from one of the clinical trial registers that have been validated in accordance with the criteria established by WHO and ICMJE. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal/Evidence for Health Care. The addresses for these registers are available from the ICMJE website (<http://www.icmje.org>). The identification number should be declared at the end of the abstract.

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>7,8</sup>
4. Systematic reviews of the literature and meta-analyses: PRISMA<sup>4</sup>

The São Paulo Medical Journal takes the view that these guidelines not only aid in writing and organizing the content of articles in a standardized manner, thereby improving their quality and facilitating reading and assessment, but also these guidelines help to avoid

situations in which important information on the methodology of studies remains outside of the manuscript.

As a partner institution of the Cochrane Collaboration and the Brazilian Cochrane Center, the *Associação Paulista de Medicina* considers that production of articles in accordance with these guidelines also aids in future production of systematic reviews of the literature and meta-analyses. Thus, articles submitted for publication that are not in accordance with these norms may be returned to their authors for adjustment before the peer review process begins.

Original articles must be structured so as to contain the following parts: Introduction, Objective, Methods, Results, Discussion and Conclusion. The text must not exceed 5,000 words (excluding tables, figures and references), from the introduction to the end of the conclusion, and must include a structured abstract with a maximum of 250 words.<sup>9</sup> "Structured abstract" means that the abstract must contain the following items: Context and objective, Design and setting, Method, Results and Conclusion.

The structure of the document should follow the format laid out below:

- 1) *Title and abstract*: the study design and/or the way participants were allocated to interventions, for example "randomized" or "retrospective" study, should be mentioned in the title and in the abstract. The abstract should provide a summary of what was done and what was found.
- 2) *Introduction*: specify the reasons for carrying out the study, describing the present state of knowledge of the topic. Describe the scientific background and "the state of the art". Do not include here any results or conclusions from the study. Use the last paragraph to specify the principal question of the study, and the principal hypothesis tested, if there is one. Do not include discussions about the literature in the introduction; the introduction section should be short.
- 3) *Objective*: describe briefly what the main objective or question of the study was. Clearly describe the pre-specified hypotheses.
- 4) *Methods*
  - 4.1) *Type of study*: describe the design of the study and specify, if appropriate, the type of randomization (the way in which draws were conducted), the blinding (how this was ensured), the diagnostic test standards (gold standard or range of normal values) and the time direction (retrospective or prospective). For example: "randomized clinical trial", "double-blind placebo-controlled clinical trial", "cross-sectional accuracy study", "retrospective cohort study", "cross-sectional prevalence study" or "systematic review of clinical trials".
  - 4.2) *Sample, participants or patients*: describe the eligibility criteria for participants (inclusion and exclusion criteria) and the sources and procedures for selection or recruitment. In case-control studies, describe the rationale for distributing the subjects as cases and controls, and the matching criteria. The numbers of patients at the beginning and end of

the study (after exclusions) must be made clear. A flow diagram showing the initial recruitment, the exclusions and the final sample of patients included should be produced and inserted in the article.

- 4.3) *Setting*: indicate the place where the study was carried out, including the type of healthcare provided (i.e. whether primary or tertiary; and whether in a private or in a public hospital). Avoid stating the name of the institution where the study was developed (for blinding purposes in the peer review). Only the type of institution should be made clear, for example: “public university hospital” or “private clinic”.
- 4.4) *Procedures* (intervention, diagnostic test or exposure): describe the principal characteristics of any intervention, including the method, the timing and the duration of its administration or of data collection. Describe the differences in interventions administered to each group (if the study is controlled). Detail the procedures in such a way that other researchers will be able to repeat them in other localities.
- 4.5) *Main measurements, variables and outcome*: state what the primary and secondary outcomes analyzed in the study are. Describe the method of measuring the primary result, in the way in which it was planned before data collection. For each variable of interest, detail the assessment methods. If the hypothesis of the study was formulated during or after data collection (and not before), this needs to be declared. Describe the methods used to enhance the quality of measurements (for example, multiple observers, training, etc.) and to avoid bias. Explain how quantitative variables were handled in the analyses.
- 4.6) *Sample size and statistical analysis*: describe the sample size calculation method, or the study period in the event that patients were consecutively admitted over a period. Readers need to understand why a given number of patients was used. The planned statistical analysis, the statistical tests used and their significance levels, along with any *post hoc* analyses, should be presented in this section. Describe the methods used to control for confounding factors and variables, and explain how missing data and cases lost from the follow-up were dealt with.
- 4.7) *Randomization*: describe the method used to implement the random allocation sequence (for example, sealed envelopes containing random sequences of numbers or software for generating random numbers). If appropriate, report that the study used “quasi-randomization”.<sup>12</sup> In addition, describe who generated the random sequence, who assigned the participants to each group (in the case of controlled trials) and who recruited the participants.
- 5) *Results*: describe the main findings. If possible, these should be accompanied by their 95% confidence intervals and the exact level of statistical significance (it is not enough to write

“ $P < 0.05$ ”: the exact P value should be supplied). For comparative studies, the confidence interval must be stated for the differences between the groups.

- 5.1) *Participant flow diagram*: describe the flow of participants through each stage of the study (inclusions and exclusions) and the follow-up period, and the number of participants completing the study (or lost from the follow-up). Use a flow diagram to demonstrate the numbers of patients, from the initial recruitment to the end of the study, and the reasons for exclusions. If there was any “intention-to-treat” analysis, describe it.
- 5.2) *Deviations*: if there was any deviation from the protocol, away from what was initially planned, describe it and the reasons for it.
- 5.3) *Adverse events*: describe any side effect, adverse event or complication.
- 6) *Discussion*: provide an interpretation of the results, taking into account the study hypotheses and conclusions. Emphasize the new and important factors encountered in the study, which will form part of the conclusion. Do not repeat data presented in the introduction or results in detail. Mention any limitations of the findings that should be noted and any possible implications for future research. Describe any potential bias. Report any relevant findings from other studies: it is important to review the recent literature to seek new evidence that may have been published, which needs to be discussed. State whether the findings can be generalized to populations (i.e. whether the findings have external validity). It is recommended that the last two paragraphs should contain implications for practice and for further research.
- 7) *Conclusions*: specify only the conclusions that can be sustained by the results, together with their clinical significance (avoiding excessive generalization). Draw conclusions based on the objectives and hypotheses of the study. The same emphasis should be placed on studies with positive and negative results.

Systematic reviews with or without meta-analyses should comply with the same publication norms established for original articles, and be produced in accordance with PRISMA<sup>4</sup> and the Cochrane Collaboration’s systematic review Handbook.<sup>13</sup> The text should not exceed 5,000 words (excluding tables, figures and references)

#### *Short communications, case reports or case series*

Short communications and case reports must be limited to 3,000 words (from the introduction to the end of the conclusion). 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 thus: Introduction, Objective, Methods, Results, Discussion and Conclusion, like in original articles.

Individual case reports should contain: 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 key words. The abstracts in short communications should be structured with: Context and objective, Design and setting, Methods, Results and Conclusion, like in original articles. The abstracts in case reports and case series should contain: Context, Case Report (with a description of the case and a pertinent discussion) and Conclusion.

The São Paulo Medical Journal/Evidence for Health Care 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>14</sup> The results from the systematic search of the main databases — Medline (via PubMed), Embase, Lilacs and Cochrane Library — should be presented in a table with the search strategy for each database and the number of articles obtained.

#### *Narrative reviews*

Narrative reviews may be accepted by the São Paulo Medical Journal/Evidence for Health Care and should be structured with: Introduction, Objectives, Methods, Results, Discussion and Conclusions. The abstract must be structured with: Context and objective, Design and setting, Methods, Results and Conclusions, like in original articles. The manuscript must comply with the norms of the Vancouver style<sup>1</sup> and must include a systematic search in the main databases: Medline, Embase, Lilacs and Cochrane Library. The search strategy for each database and the number of articles obtained from each database should be presented 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 must be used for Medline, LILACS and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, search strategy must be performed, at the same time, with English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms. 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).

#### *Letters to the editor*

Letters to the editor may address articles published in the São Paulo Medical Journal/Evidence for Health Care publication or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

#### **Documents cited**

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