ISSN 1516-3180

São Paulo Medical Journal/Evidence for Health Care, 2018 February 1; 136(1):1-96

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

Medline, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/ Sciences Edition (impact factor 0.929) and EBSCO Publishing

February 1 - Volume 136 - Number 1

Cross-sectional study:

- Association between frailty and violence against community-dwelling elderly people in Brazil

Prospective three-year Longitudinal study:

- C-reactive protein/albumin ratio is associated with lung function among children/adolescents with cystic fibrosis

Randomized single-blind controlled trial:

- Sensory-motor training versus resistance training among patients with knee osteoarthritis

Review of systematic reviews:

- What do Cochrane systematic reviews say about non-surgical interventions for urinary incontinence in women?

Basílica de Nossa Senhora da Penha
cifotart/ shutterstock.com.com

São Paulo Medical Journal does not charge authors for publication.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Federada da AMB Associação Médica Brasileira

Que tal reunir os amigos e a família em um final de semana no nosso Clube de Campo?

Hospede-se em um dos deliciosos chalés e aproveite ao máximo todo o incrível visual em meio à Mata Atlântica intocada.

CLUBE DE CAMPO APM

Saiba mais:
Tels: (11) 4899-3535 / 18 / 19 / 36
e-mail: sedecampestre@apm.org.br
Horário de atendimento: 9h às 18h
Endereço: Estrada de Santa Inês, Km 10 - Caieiras, SP

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

São Paulo Medical Journal
EVIDENCE FOR HEALTH CARE

INDEX

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Correspondence to:

ASSOCIAÇÃO PAULISTA DE MEDICINA
Publicações Científicas
Av. Brig. Luís Antônio, 278 - 7º andar –
São Paulo (SP) – Brasil – CEP 01318-901
Tel. (+55 11) 3188-4310/3188-4311
E-mail: revistas@apm.org.br

www.scielo.br/spmj

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES

ORGANIZATION

Founded in 1932, a bimonthly publication of the Associação Paulista de Medicina
e-mail: revistas@apm.org.br

Editors: Álvaro Nagib Atallah and Paulo Andrade Lotufo.
Editorial advisor: Rachel Riera.
Editorial assistant: Marina de Britto.
Scientific journalist and editor: Patrícia Logullo (MTB: 2-6.152).
Associate editors: Adriana Seber, Aécio Flávio Teixeira de Góis, Airton Tetelbom Stein, Alexander Wagner Silva de Souza, Antonio José Gonçalves, Aytan Miranda Sipahi, Cristina Muccioli, Delcio Matos, Domingo Marcolino Braile, Edina Mariko Koga da Silva, Fernando Antonio de Almeida, Flávio Faloppa, Heráclito Barbosa de Carvalho, José Antônio Rocha Gontijo, José Carlos Costa Baptista-Silva, José Maria Soares Júnior, José Roberto Lapa e Silva, Laércio Joel Franco, Maria do Patrocínio Tenório Nunes, Milton de Arruda Martins, Moacir Fernandes de Godoy, Olavo Pires de Camargo, Renato Corrêa Baena, Sergio Tufik, Vania dos Santos Nunes.
Proofreading: David Elliff.
Desktop publishing: Zeppelini Editorial (www.zeppelini.com.br).
Listed in: Medline, Lilacs, SciELO, Science Citation Index Expanded and Journal Citation Reports/Sciences Edition (impact factor 0.588) and EBSCO publishing.
International Board: Alexandre Wagner Silva de Souza (University Medical Center Groningen, Groningen, Netherlands), Charles J. Menkes (Cochin Hospital, Paris, France), José Fragata (CUF Infante Santo Hospital, Lisbon), Luiz Dratcu (Guy's Hospital, London, and Maudsley NHS Trust, York Clinic, London), Marcelo Cypel (University Health Network, Toronto, Canada), Karla Soares-Weiser (Enhance Reviews Ltd, Wantage, United Kingdom), Tirone Espiridião David (Toronto General Hospital, Toronto, Canada), Mário Viana de Queiroz (Hospital de Santa Maria, Lisbon), Wadih Arap (MD Anderson Cancer Center, University of Texas, Houston, United States), Wellington V. Cardoso (Boston University, Boston, United States).

• SPMJ website: access to the entire São Paulo Medical Journal/Revista Paulista de Medicina website is free to all. We will give at least six months notice of any change in this policy. SPMJ printed version: six issues/year; 1 volume/year, beginning on first Thursday in January.

• One-year subscription for the year 2018: individual US$ 195; institutional US$ 260.

Scientific Council

Diretoria Executiva da Associação Paulista de Medicina (Triênio 2017-2020)

Keeping a watchful eye on the food giants and cleansing the temple of nutritional medicine and epidemiology

Paulo Andrade Lotufo[I]

Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo (SP), Brazil

[I]MD, DrPH. Full Professor, Department of Internal Medicine, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo (SP), Brazil.
orcid.org/0000-0002-4856-8450

One of the most-loved enemies of medical editors, healthcare policy planners, scholars and scientists in the fields of medicine and public health is the companies that are known as "big pharma." Indeed, our attitude is correct, because these companies keep on pushing products that lead to addiction to opioids and fentanyl (not unlike the addiction to heroin that is perpetrated by "traditional" drug dealers)[1] and indulge in disease-mongering such as highlighting testosterone insufficiency in males.[2-3] Two former editors of the *New England Journal of Medicine*, Marcia Angell and Jerome Kassirer, described in detail how "big pharma" works. Their reports did not receive any credible rebuttal from the pharmaceutical companies.[4-5]

However, over the last two decades, the scientific community has been curbing the bad behavior of "big pharma." Governments have demanded that medical associations should implement compliance policies regarding publicization and commercialization of pharmaceutical products during congresses and events. For talks and papers, disclosure of conflicts of interest by lecturers and authors has become the reality, and there is no chance of turning the clock back. The most important stance certainly came from the International Committee of Medical Journal Editors, when it determined that all randomized clinical trials should be preregistered on public websites before the beginning of participant enrolment, such that this would be a *sine qua non* condition for further publication in any journal.[6]

While "big pharma" loves to push its products, most of these are, in reality, at breakthrough point, as has been seen in relation to statins. On the other hand, the community of editors, public health planners, scholars and scientists in the fields of medicine and public health has been negligent in relation to the actions of the food industry. The community has acted as well-wishers in relation to "alternative" diets. This attitude is erroneous and constitutes a typical double standard.

There is no reason why a critical attitude should not be adopted in relation to the food industry, alternative diets and published papers addressing diets that apply inadequate tools or meta-analyses. In contrast to current levels of understanding of the workings of big pharma, medical journals are less familiar with descriptions of how "big food" works.

The lay press has sometimes adopted a more critical approach than have scientific journals. One example can be seen in a book by Michael Moss called "Salt, sugar, fat: how the food giant hooked us," which forms a summary of a series of articles by this author that were published in the New York Times.[7] Recently, this newspaper published an excellent four-page description of how major companies like Nestlé operate in Brazil, with sales of high-caloric foods to poor people.[8]

Separately, but with similar bias, physicians, dietitians and physical educators have created a very profitable activity through selling books and cookbooks and giving very well rewarded lectures that mostly address foolish theories relating to diet.[9] One of the worst examples of this comes from an overrated Brazilian physician who demonizes statins and at the same time uses this to sell his fad diet books. A review of 206 industry-funded studies found a a sevenfold greater chance of a favorable conclusion than of an unfavorable conclusion, in comparing those fully funded by the food industry with those without such funding, respectively.[10] Furthermore, the same comparison showed a "bias factor" of 3.6 for funded studies![11]

However, within the traditional scientific field of nutritional epidemiology, there is a terrible mess. Recently, a cohort study with dubious results regarding connections between fat and heart

disease confidently claimed that the accumulated conclusions from decades of knowledge acquired through large observational studies should be dismissed. The authors' conclusion was very pretentious, stating that "global dietary guidelines should be reconsidered in the light of these findings."[12]

Meta-analyses have been useful for assessing issues relating to treatments, but they are not an appropriate tool for observational studies relating to diets used in different times and places.[13] More than eight decades of studies showing that consumption of foods containing animal fat was associated with atherosclerosis and cardiovascular events were "invalidated" through a meta-analysis claiming that "butter is back" (in fairness, the authors did not state this,[14,15] but it was consequently expressed thus on the cover of Time magazine).[16] Barnard et al.[13] concluded: "the food industry is well aware of the power of science-driven headlines and has invested in meta-analyses. In the process, nutritional science may be adversely affected."

Interestingly, contestation of knowledge is a one-way street. In contrast to some innovative hypotheses such as NOVA,[17] a proposal launched by Brazilian scientists was contested in a bitter editorial from the American Journal of Clinical Nutrition, in which the first author disclosed that he "serves on scientific committees for Nestlé and Cereal Partners Worldwide."[18] The journal did not accept the rebuttal from NOVA's proponents, who needed to publish it elsewhere.[19]

In conclusion, we need to continue to keep a watchful eye on big pharma, while, at the same time, doing this with the same vigor in relation to the "food giants" and "cleansing the temple" of medicine and epidemiology relating to diet and nutrition.

REFERENCES

1. Alexander B. When a Company is Making Money from the Opioid Crisis. The Atlantic Sept 6, 2017. Available from: https://www.theatlantic.com/business/archive/2017/09/opioid-crisis-responsibility-profits/538938/. Accessed in 2018 (Dec 13).
2. Payer L. Disease-Mongers: How Doctors, Drug Companies, and Insurers are Making You Feel Sick. New Jersey, USA: John Wiley & Sons; 1992. ISBN 0-471-00737-4.
3. Vitry AI, Mintzes B. Disease mongering and low testosterone in men: the tale of two regulatory failures. Med J Aust. 2012;196(10):619-21. PMID: 22676868.
4. Angell M. The Truth about the Drug Companies: How they deceive us and what to do about it. New York: Random House; 2004. ISBN: 0-375-50846-5.
5. Kassirer JP. On the Take: How Medicine's Complicity with Big Business Can Endanger Your Health. United Kingdom: Oxford University Press; 2005. ISBN13: 978-0195300048.
6. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. Ann Intern Med. 2004;141(6):477-8. PMID: 15355883.
7. Moss M. Salt, sugar, fat: how the food giant hooked us. New York: Random House; 2014.
8. Jacobs A, Richtell M. How Big Business Got Brazil Hooked on Junk Food. The New York Times, Sep 16, 2017. Available from: https://www.nytimes.com/interactive/2017/09/16/health/brazil-obesity-nestle.html. Accessed in 2018 (Dec 13).
9. Ioannidis JPA, Trepanowski JF. Disclosures in Nutrition Research. Why is it Different? JAMA. 2017. doi:10.1001/jama.2017.18571.
10. Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Med. 2007;4(1):e5. doi: 10.1371/journal.pmed.0040005.
11. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289(4):454-65. PMID: 12533125.
12. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017;390(10107):2050-62. doi: 10.1016/S0140-6736(17)32252-3.
13. Barnard ND, Willett WC, Ding EL. The Misuse of Meta-analysis in Nutrition Research. JAMA. 2017;318(15):1435-36. doi: 10.1001/jama.2017.12083.
14. Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160(6):398-406. doi: 10.7326/M13-1788.
15. Pimpin L, Wu JH, Haskelberg H, Del Gobbo L, Mozaffarian D. Is Butter Back? A Systematic Review and Meta-Analysis of Butter Consumption and Risk of Cardiovascular Disease, Diabetes, and Total Mortality. PLoS One. 2016;11(6):e0158118. doi: 10.1371/journal.pone.0158118.
16. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Prospective Urban Rural Epidemiology (PURE) study investigators. Lancet. 2017;390(10107):2050-2062. doi: 10.1016/S0140-6736(17)32252-3.
17. Monteiro CA, Cannon G, Moubarac JC, et al. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr. 2018;21(1):5-17. doi: 10.1017/S1368980017000234.
18. Gibney MJ, Forde CG, Mullally D, Gibney ER. Ultra-processed foods in human health: a critical appraisal. Am J Clin Nutr. 2017 Sep;106(3):717-24. doi: 10.3945/ajcn.117.160440.
19. Monteiro CA, Cannon G, Moubarac JC, et al. Ultra-processing. An odd 'appraisal'. Public Health Nutr. 2017:1-5. doi: 10.1017/S1368980017003287.

Sources of funding: Recipient of a grant as an established researcher, from Conselho Nacional de Pesquisa, Brasília, Brazil

Conflict of interest: Indirect: honoraria from AbbVie Brazil and Amgen Brazil for lectures; direct: research grants from Fundação Vale, Rio de Janeiro, Brazil

Address for correspondence:
Paulo Andrade Lotufo
Centro de Pesquisa Clínica e Epidemiológica, Hospital Universitário,
Universidade de São Paulo
Av. Prof. Lineu Prestes, 2.565
Butantã — São Paulo (SP) — Brasil
Tel. (+55 11) 3091-9300
E-mail: palotufo@usp.br

DOI: 10.1590/1516-3180.2017.0098070817

Accidents involving motorcycles and potential years of life lost. An ecological and exploratory study

Drielle Rezende Pavanitto[I], Renata Armani de Moura Menezes[I], Luiz Fernando Costa Nascimento[II]

Department of Medicine, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil

[I]Medical Student, Department of Medicine, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil.

[II]PhD. Researcher, Department of Energy, Universidade Estadual Paulista (UNESP), Guaratinguetá (SP), and Assistant Professor, Department of Medicine, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil.

KEY WORDS:
Life expectancy.
Geographic information systems.
Motorcycles.
Accidents, traffic.

ABSTRACT

CONTEXT AND OBJECTIVE: Traffic accidents have gained prominence as one of the modern epidemics that plague the world. The objective of this study was to identify the spatial distribution of potential years of life lost (PYLL) due to accidents involving motorcycles in the state of São Paulo, Brazil.

DESIGN AND SETTING: Ecological and exploratory study conducted in São Paulo.

METHODS: Data on deaths among individuals aged 20-39 years due to motorcycle accidents (V20-V29 in the International Classification of Diseases, 10th revision) in the state of São Paulo in the years 2007-2011 were obtained from DATASUS. These data were stratified into a database for the 63 microregions of this state, according to where the motorcyclist lived. PYLL rates per 100,000 inhabitants were calculated. Spatial autocorrelations were estimated using the Global Moran index (IM). Thematic, Moran and Kernel maps were constructed using PYLL rates for the age groups of 20-29 and 30-39 years. The Terraview 4.2.2 software was used for the analysis.

RESULTS: The PYLL rates were 486.9 for the ages of 20-29 years and 199.5 for 30-39 years. Seventeen microregions with high PYLL rates for the age group of 20-29 years were identified. There was higher density of these rates on the Kernel map of the southeastern region (covering the metropolitan region of São Paulo). There were no spatial autocorrelations between rates.

CONCLUSIONS: The data presented in this study identified microregions with high accident rates involving motorcycles and microregions that deserve special attention from regional managers and traffic experts.

INTRODUCTION

Brazil occupies the fifth place among the countries with the highest numbers of traffic deaths, only preceded by India, China, the United States and Russia. The mortality rate due to road transport accidents (RTAs) increased from 18.0 to 22.5 deaths/100,000 inhabitants between 2000 and 2010, which represented an increase of 32.3% over this decade.[1] The motorcycle accident mortality rate in Brazil increased from 0.5 to 4.5/100,000 inhabitants from 1996 to 2009, which represented an increase of 800% over this period.[2] Collisions between motorcycles and automobiles was the largest cause of these accidents (38.4%) and accidental falls from motorcycles was the second (32%), in a survey on 378 recorded incidents involving motorcycle accidents in Corumbá, Mato Grosso do Sul, in 2010.[3] Motorcycle accidents are highly worrisome, since they mainly affect young people of economically active age, with a high chance of death,[4] as shown in the state of Sergipe, among 554 motorcycle accident victims who were attended at a referral center.[5]

In the western region of the Paraíba valley, in the state of São Paulo, a cluster of nine municipalities with the highest hospitalization rates due to motorcycle accidents was identified through spatial analysis.[6] This approach, including the indicator of potential years of life lost (PYLL), was used in the state of Pernambuco, in the year 2007, for a study on accidents due to RTAs. It was found that 13,196 RTAs involved motorcycles, which represented 27. 5% of the total number of accidents.[7] The PYLL indicator estimates the impact of deaths on society. It qualifies deaths and presents a new criterion for selecting priorities. Through a single figure, the PYLL indicator covers the magnitude of the impact, expressed as the number of deaths according to the age at which the event occurs, and the vulnerability to death. Thus, this indicator quantifies mortality not only according to the frequency of occurrence of death but also according to the time left to live, up to the limit of life expectancy.

Spatial analysis is a geostatistical tool that is becoming widely used in research, including in health-related fields. One of its applications encompasses identification of spatial clusters, i.e. any aggregations of events that are not merely random. Through developing maps, the aim is to analyze whether the distribution of these events actually presents a spatial pattern, or whether it is random. In addition, these data can be used by other sectors, such as transport-related education and inspection, and may serve as a basis for reducing the risk of accidents. Thus, one of the indications for using spatial analysis is to identify sites with greater intensity of accidents, i.e. critical areas. This can serve as backing for implementation of prevention and control measures, as presented in several recent articles published in Brazil.[6,8-11]

OBJECTIVE

Considering the increasing number of motorcycles that form part of the vehicle fleet, the vulnerability of motorcyclists and their possible pillion passengers and the age group to which most motorcyclists belong, the purpose of this study was to identify the spatial distribution of PYLL in the microregions of the state of Sao Paulo, according to accidents involving motorcycles from 2007 to 2011.

METHODS

An exploratory ecological study was conducted using spatial analysis tools, on mortality data relating to accidents involving motorcycles in the state of São Paulo, Brazil, according to its 63 microregions. The mortality data were obtained from the Mortality Information System (SIM), which includes data from death certificates from all over the country and is available through the website of the Department of Information Technology of the Brazilian National Health System (DATASUS).[12] The period examined was from January 1, 2007, to December 31, 2011, and the age groups covered were 20 to 29 years and 30 to 39 years. The diagnoses considered related to accidents involving motorcyclists (V20-V29 of the International Classification of Diseases, 10th revision).

The sizes of the populations within these age strata (20-39 years of age) over this period were ascertained and mortality rates per 100,000 inhabitants were calculated, to make it possible to compare PYLL values between the microregions. Five-year periods were used to minimize possible fluctuations in death data. The population estimates used were obtained from the DATASUS website.[12]

The technique for PYLL estimation proposed by Romeder and McWhinnie was used,[13] as expressed in the following mathematical formula:

$$PYLL = \Sigma\ (70 - i - 0.5)\ di$$

where i was taken to be the midpoint of the intervals from 20 to 29 years and from 30 to 39 years for each group, and di was the number of deaths in each microregion, according to age group.

The PYLL rates for the age groups of 20 to 29 years and 30 to 39 years were calculated to ensure comparability with other studies on populations of different sizes and populational pyramids. The following mathematical formula, adapted from Romeder and McWhinnie, was used:[13]

$$\text{PYLL rate} = (\text{PYLL}/N) * 100{,}000 \text{ inhabitants}$$

where N = the number of people in the corresponding age group.

The age limit of 70 years was chosen because this was the age proposed in the original method.

These values were inserted in a digital map of the state of São Paulo according to its microregions, which was obtained from the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE). Thematic maps were then constructed using the PYLL values for the ranges of 20-29 years and 30-39 years. In addition to the thematic maps, Kernel maps containing quartic function, density calculation, adaptive radius and 200 columns were constructed; these maps analyzed the behavior of dot patterns. Thus, through interpolation, the Kernel maps provided point intensities relating to the process, throughout the study region. From this, an overview of the areas of higher density of PYLL was obtained.[14]

Box maps were another form of graphical representation that was used. In this, correlations were made between Z (normalized values) and Wz values (averages of neighbors) in scatter plots divided into quadrants (Q). The Q values ranged from 1 to 4, such that Q1 corresponded to high-high values (i.e. high values of Z and high values of Wz); Q2, low-low; Q3, high-low; and Q4, low-high.[14]

The statistical analysis was based on calculation of the Global Moran Index (IM) for motorcycle riders' PYLL rates. This index indicates the degree of spatial association in the information set, from the product to the mean, thus providing a single value as a measure of the spatial association for the entire data set. The values for this index, which is an overall measurement of spatial autocorrelation, are contained within the interval [-1; 1]. In calculating this index, it is important to establish its statistical validity by estimating its significance (P-value). Values close to zero indicate a lack of significant spatial autocorrelation between the values of the variables. Positive and negative values indicate positive or negative self-correlations between variables, respectively.[14]

The TerraView v4.2.2 public-access software developed by the National Institute of Space Research (Instituto Nacional de Pesquisas Espaciais, INPE) was used for the statistical analysis. Because this was an ecological study without the possibility that its subjects might be identified, it was not submitted to a research ethics committee for approval.

RESULTS

A total of 5,348 deaths in the age range of 20 to 39 years over the years 2007 to 2011 were identified in the 63 microregions of the state of São Paulo. Of these, 3,686 deaths (68.9%) occurred in the age group of 20-29 years and 1,662 deaths (31.1%) in the age group of 30-39 years. There were 4,885 deaths of males (91.3%).

The mortality coefficients according to age group were 10.04 deaths/100,000 inhabitants for the range of 20-29 years and 4.96/100,000 inhabitants for the range of 30-39 years of age.

Table 1. Descriptive analysis on age group variables (years) with mean, standard deviation (SD), minimum (Min) and maximum (Max) values for potential years of life lost, and the Moran index (IM) with respective P-values, state of São Paulo, 2007-2011

Age group	Mean (SD)	Min-Max	IM (P-value)
20-29	486.9 (231.6)	98.1-1134.0	0.01 (0.41)
30-39	199.5 (105.5)	23.7-568.6	-0.04 (0.28)

Table 1 shows that the mean PYLL rate among the population living in the state of São Paulo aged 20-29 years old was almost double that of the population aged 30-39 years. The minimum and maximum were also practically double in the 20-29 years population but the Moran indices for these age groups were not significantly different.

Figure 1 shows the thematic maps of PYLL rates per 100,000 inhabitants for accidents involving motorcyclists aged 20-29 years (**Figure 1A**) and 30-39 years (**Figure 1B**). The highest contribution to these rates was the age group of 20 to 29 years, in which 38 microregions presented rates greater than 400 PYLL/100,000 inhabitants.

The Kernel maps show high densities of PYLL rates in microregions located in the metropolitan region of São Paulo and also in its surroundings, such as in Sorocaba, Osasco, Campinas, Jundiaí, Itapecerica da Serra, Franco da Rocha, Bragança Paulista and Piedade, for the age groups of 20-29 and 30-39 years (**Figures 2A** and **2B**).

Figure 3 presents Box maps that depict the microregions of high priority (HIGH), low priority (LOW) and no statistical significance

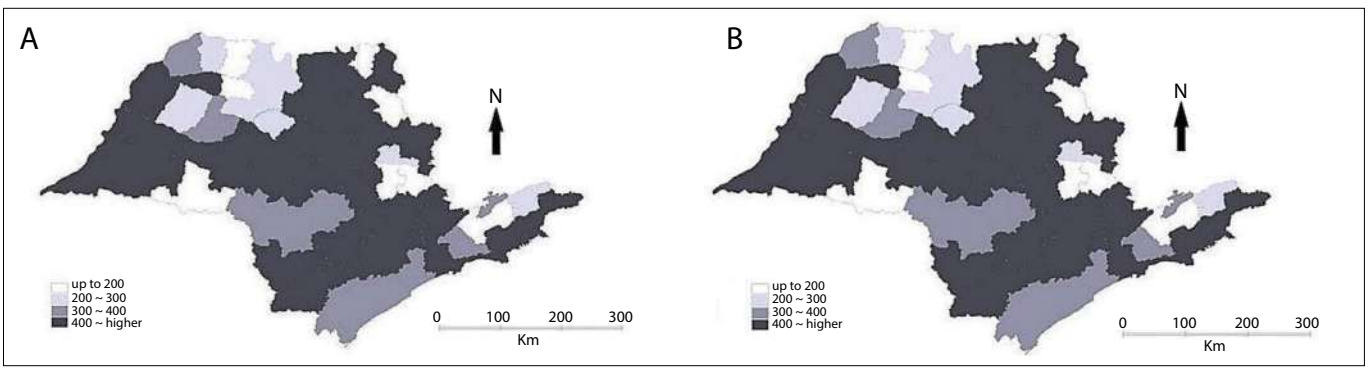


Figure 1. Rates of potential years of life lost per 100,000 inhabitants among motorcyclists aged 20-29 years (**A**) and 30-39 years (**B**), according to microregions of the state of São Paulo, 2007-2011.

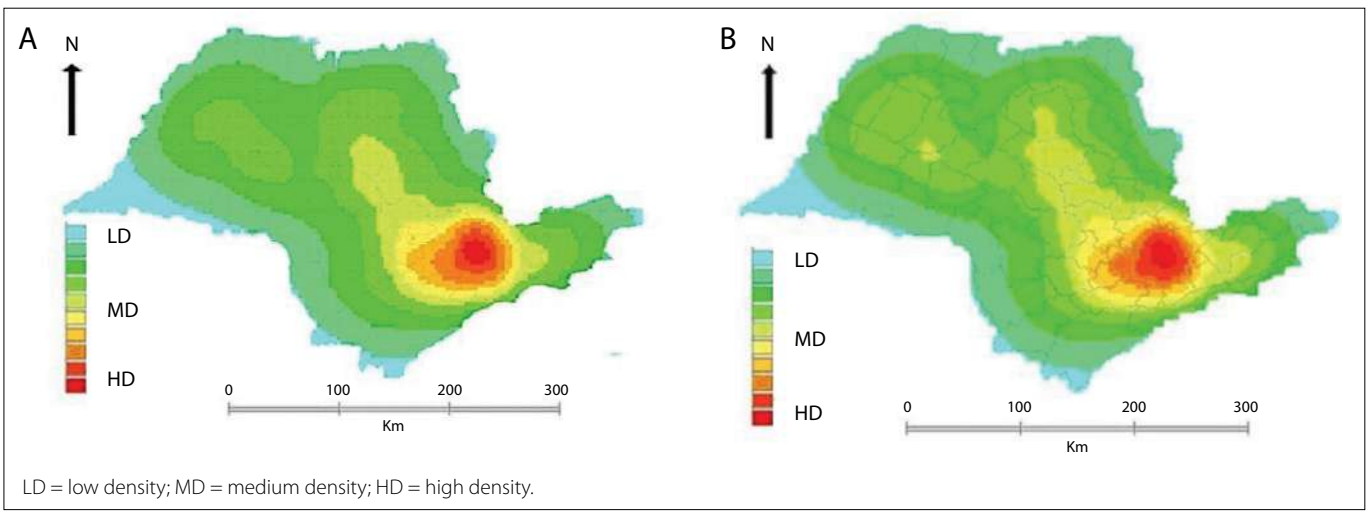


Figure 2. Kernel maps showing densities of rates of potential years of life lost per 100,000 inhabitants, among motorcyclists aged 20-29 years (**A**) and 30-39 years (**B**), according to microregions of the state of São Paulo, 2007-2011.

(NS) regarding their PYLL rates per 100,000 inhabitants. **Figure 3A** shows the PYLL rates for the age group of 20 to 29 years old, and indicates that 17 microregions have high priority for interventions; while **Figure 3B** shows the PYLL rates for the age group of 30-39 years, and indicates that 14 microregions have high priority for interventions.

DISCUSSION

To the best of our knowledge, this was the first study conducted using data from the state of São Paulo, thus making it difficult to compare this study with different places and times. In this study, greater concentration of accidents was identified in the metropolitan region of São Paulo and also in the microregions of Sorocaba, Osasco, Campinas, Jundiaí, Itapecerica da Serra, Franco da Rocha, Bragança Paulista and Piedade. Moreover, it was possible to identify microregions with high PYLL rates that deserve high-priority interventions to minimize these rates, to be implemented by regional managers and authorities linked to traffic management, given that these rates show the high impact of deaths within an economically active age range.

This study focused on a spatial approach to potential years of life lost by specifically addressing motorcycle accidents. Traffic accidents involving motorcycles in the state of São Paulo are worrying. In 2012, there were 1,700 deaths due to motorcycle accidents in the state of São Paulo and 1,200 (approximately 71%) occurred in the age group of 20-39 years, which is a young and economically active segment of the population. In our study, around 71% of the accidents involving motorcycles occurred among individuals in this age group, with higher prevalence among males (91.3%).[12]

The approach used here, i.e. spatial analysis, has been applied in many public health studies such as those describing accidents involving motorcyclists in Maringá, Paraná,[4] and in the Paraíba valley, state of São Paulo,[6] and in studies on other topics such as the spatial distribution of cesarean section rates in the state of São Paulo,[9] Alzheimer's deaths in the state of São Paulo[10] and pneumonia in the Paraíba valley, state of São Paulo.[11]

A study conducted in the state of Pernambuco, in 2007, brought together spatial analysis and PYLL in relation to motorcycle accidents. It found that the mean number of PYLL due to RTA was 35.1 years, and that among the victims, 27.5% were motorcyclists, 24.6% were pedestrians and 17.82% were car occupants.[7]

In Rio Branco, Acre, the number of accidents involving motorcycles and the number of victims have been correlated with the growth of the fleet of motorcycles, which increased by 42.2% over the study period, while the fleet of other vehicle types increased by 9.2%. These accidents predominantly involved males and the age groups of 20 to 29 and 30 to 39 years.[15]

The Brazilian fleet of motorcycles increased from approximately 2,800,000 in 1998 to 16,500,000 in 2010, which was an increase of 490%.[2] This increase, which resulted from marketing actions promoted by manufacturers and resellers, from low purchase prices associated with the introduction of long-term financing for instalment plans with small monthly repayments, and from use of motorcycles as a work tool for an increasing range of professional activities, may have contributed towards the increase in the number of accidents. Nevertheless, other causes may be correlated with this increase, including a lack of safety measures such as roads that are not always well maintained, riders' carelessness in traffic, negligence regarding the quality and validity of helmets (which have a maximum useful life) and lack of supervision by the highway authorities regarding motorcycle and rider conditions.[1,4]

The data presented in this study coincide with the findings of Silva et al., who used spatial analysis in a study carried out in the state of Pernambuco, where the highest death rates involving motorcyclists formed urban clusters, including in the metropolitan region of Recife. Both studies showed higher rates of PYLL among in male motorcyclists and in the age group of 20-39 years.[16]

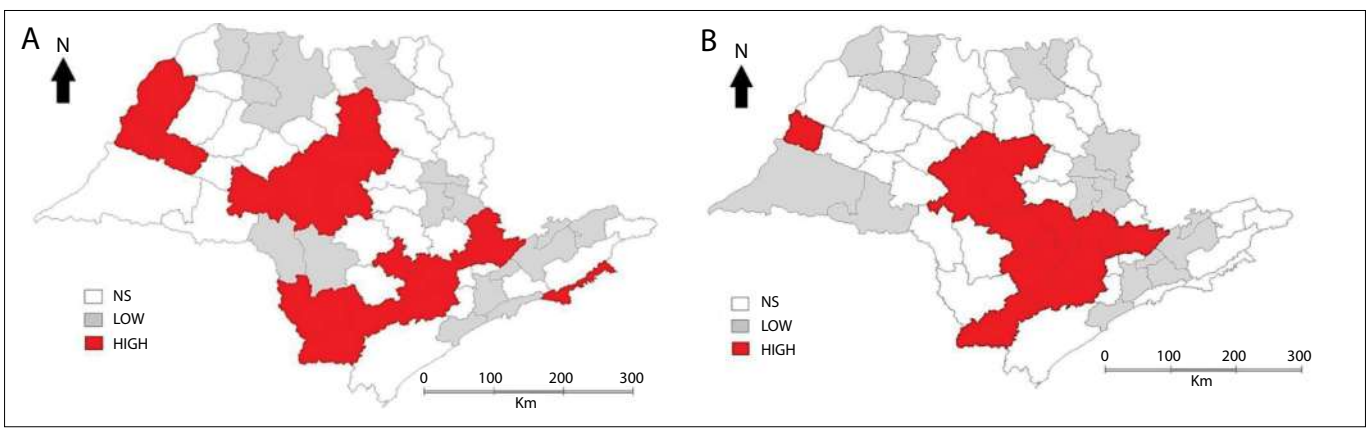


Figure 3. Box maps showing microregions that present high priority for interventions (HIGH), low priority (LOW) and no statistical significance (NS), according to potential years of life lost per 100,000 inhabitants, involving motorcyclists aged 20-29 years (**A**) and 30-39 years (**B**); state of São Paulo, 2007-2011.

Our findings also coincide with those of Andrade and Mello-Jorge,[17] who identified a loss of more than 1.3 million years due to terrestrial transport accidents over the years 2011 to 2013. They indicated that the age group that was most compromised was from 20 to 39 years, which accounted for 760,000 PYLL (around 60% of the total), of which 650,000 PYLL (around 86% in 20-39 age strata) related to males. The death rate per 100,000 inhabitants was highest (6.3) among motorcyclists. These authors showed that the costs were of the order of R$ 115 million (approximately US$ 30 million), which corresponded to 50% of the total expenses incurred through hospitalizations due to road traffic accidents and to 550,000 days of hospitalization due to traffic accidents involving motorcycles in 2012.[18]

Mascarenhas et al. evaluated records from emergency services in 24 state capitals and from the national capital (Brasília) relating to transportation accidents involving motorcyclists. They found that 66% of these admissions related to victims between 20 and 39 years of age, which was a rate similar to what was found in our study.[19]

In a time series study conducted using data from the state of Santa Catarina, among 19,889 motorcycle accidents, 84.43% of these involved male victims. The age groups of 20 to 29 years and 30 to 39 years accounted for a total of 10,564 hospitalizations (around 53%).[20]

Accidents involving motorcycles accounted for around 12% of all deaths in the age group 20-29 years old in our study. In total, males were much more affected (around 90%).[12]

The present study may have limitations and among these, it needs to be pointed out that the data used were secondary, although they were obtained from an official source (DATASUS). On the other hand, no information was available regarding whether deaths occurred at the accident site or at hospital shortly after the accident, or whether they occurred later on, as a result of complications from the injuries suffered by the motorcyclist. No information regarding whether the accidents occurred on highways or on the streets of the municipalities that make up the microregions studied was available. The systems compromised by the accident, such as skull trauma and fractures of upper and/or lower limbs, and the complications resulting from these injuries, have not been studied. In addition, ecological study designs do not indicate causality, but on the other hand they provide information to generate hypotheses. Nevertheless, the fact that microregions with high rates of lost years of life were identified through the present study is enough to activate regional and municipal managers to seek to discover the possible reasons that are leading to these disastrous findings.

CONCLUSIONS

From the data of the present study, it can be concluded that the number of years of life lost through occurrences of motorcycle accidents in this young age group (20-39 years of age) constitutes an important social and public health problem. The spatial approach proved to be a useful tool for identifying microregions that deserve attention and provides backing for implementation of local and regional policies to minimize these accident rates.

REFERENCES

1. Morais Neto OL, Montenegro MM, Monteiro RA, et al. Mortalidade por acidentes de transporte terrestre no Brasil na última década: tendência e aglomerados de risco [Mortality due to road traffic accidents in Brazil in the last decade: trends and risk clusters]. Ciênc Saúde Colet. 2012;17(9):2223-36.
2. Martins ET, Boing AF, Peres MA. Mortalidade por acidentes de motocicleta no Brasil: análise de tendência temporal, 1996-2009 [Motorcycle accident mortality time trends in Brazil, 1996-2009]. Rev Saúde Pública. 2013;47(5):931-41.
3. Ganne N, Martinez AT, Rodrigues C, Delgado MUC, Souza FA. Estudo sobre acidentes de trânsito envolvendo motocicletas, ocorridos no Município de Corumbá, Estado de Mato Grosso do Sul, Brasil, no ano 2010 [Motorcycle accidents in the Municipality of Corumbá, Mato Grosso do Sul State, Brazil, in 2010]. Rev Pan-Amaz Saúde. 2013;4(1):15-22
4. Oliveira NLB, Sousa RMC. Fatores associados ao óbito de motociclistas nas ocorrências de trânsito [Factors associated with the death of motorcyclists in traffic accidents]. Rev Esc Enferm USP. 2012;46(6):1379-86.
5. Vieira RCA, Hora EC, Oliveira DV, Vaez AC. Levantamento epidemiológico dos acidentes motociclisticos atendidos em um Centro de Referência ao Trauma de Sergipe [An epidemiological survey on motorcycle accident victims assisted at a Reference Trauma Center of Sergipe]. Rev Esc Enferm USP. 2011;45(6):1359-63.
6. Nunes MN, Nascimento LFC. Internações hospitalares por acidentes de moto no Vale do Paraíba [Hospitalization due to motorcycle accidents in the Paraiba Valley using spatial analysis]. Rev Assoc Med Bras. 2010;56(6):684-7.
7. Almeida APB, Lima MLC, Oliveira Júnior FJM, Abath MB, Lima MLLT. Anos potenciais de vida perdidos por acidentes de transporte no Estado de Pernambuco, Brasil, em 2007 [Potential years of life lost because of road traffic accidents in Pernambuco state, Brazil, 2007]. Epidemiol Serv Saúde. 2013;22(2):235-42.
8. Lucena RM, Sousa JL. Anos potenciais de vida perdidos (APVP) por Aids: Pernambuco, 1996 e 2005 [Years of potential life lost (YPLL) by Aids: Pernambuco, 1996 and 2005]. DST J Bras Doenças Sex Transm. 2009;21(3):136-42.
9. Campi SFS, Nascimento LFC. Distribuição espacial das cesarianas no Estado de São Paulo [Spatial distribution of C-sections within the State of São Paulo]. Rev Assoc Med Bras. 2014;60(5):419-23.
10. Almeida MC, Gomes CM, Nascimento LF. Spatial distribution of deaths due to Alzheimer's disease in the state of São Paulo, Brazil. Sao Paulo Med J. 2014;132(4):199-204.
11. Venâncio TS, Tuan TS, Nascimento LFC. Incidência de tuberculose em crianças no estado de São Paulo, Brasil, sob enfoque espacial [Indidence of tuberculosis in children in the state of São Paulo, Brazil, under spatial approach]. Ciên Saúde Coletiva. 2015;20(5):1541-7.

12. Brasil. Ministério da Saúde. Departamento de Informática do SUS (Datasus). Available from: http://www2.datasus.gov.br/DATASUS/index.php. Accessed in 2017 (Apr 6).
13. Romeder JM, McWhinnie JR. Años de vida potencial perdidos entre las edades de 1 y 70 años: un indicador de mortalidad prematura para la planificación de la salud. In: Buck C, Llopis A, Nájera E, Terris M, orgs. El desafío de la epidemiología: problemas y lecturas seleccionadas. Washington: Organización Panamericana de la Salud; 1988. p. 254-63. Available from: http://www.saludcolectiva-unr.com.ar/docs/SC-122.pdf. Acessed in 2017 (Sep 28).
14. Neves MC, Ramos FR, Camargo ECG, Câmara G, Monteiro AM. Análise exploratória espacial de dados sócio-econômicos de São Paulo. Available from: www.dpi.inpe.br/gilberto/papers/marcos_gisbrasil2000.pdf. Accessed in 2017 (Sep 6).
15. Rocha GS, Schor N. Acidentes de motocicleta no município de Rio Branco: caracterização e tendências [Motorcycle accidents in the municipality of Rio Branco in the State of Acre: characterization and trends]. Ciênc Saúde Colet. 2013;18(3):721-31.
16. Silva PHNV, Lima MLC, Moreira RS, Souza WV, Cabral APS. Estudo espacial da mortalidade por acidentes de motocicleta em Pernambuco [Spatial study of mortality in motorcycle accidents in the state of Pernambuco, northeastern Brazil]. Rev Saúde Pública. 2011;45(2):409-15.
17. Andrade SSCA, Mello-Jorge MHP. Mortalidade e anos potenciais de vida perdidos por acidentes de transporte no Brasil, 2013 [Mortality and potential years of life lost by road traffic injuries in Brazil, 2013]. Rev Saúde Pública. 2016;50:59.
18. Andrade SSCA, Jorge MHPM. Internações hospitalares por lesões decorrentes de acidente de transporte terrestre no Brasil, 2013: permanência e gastos [Hospitalization due to road traffic injuries in Brazil, 2013: hospital stay and costs]. Epidemiol Serv Saúde. 2017;26(1):31-8.
19. Mascarenhas MDM, Souto RMCV, Malta DC, et al. Características de motociclistas envolvidos em acidentes de transporte atendidos em serviços públicos de urgência e emergência [Characteristics of motorcyclists involved in road traffic accidents attended at public urgent and emergency services]. Ciên Saúde Coletiva. 2016;21(12):3661-71.
20. Schneider IJC, Schütz MV, Nazário NO, et al. Tendência das internações por acidentes motociclísticos em homens de 20 a 39 anos no Estado de Santa Catarina - Sul do Brasil [Trends in hospitalizations due to motorcycle accidents involving men aged 20 to 39 years in the state of Santa Catarina - Southern Brazil]. Cad Saúde Colet. 2017;25(2):233-41.

Conflict of interest: None
Sources of funding: None

Date of first submission: April 6, 2017
Last received: August 2, 2017
Accepted: August 7, 2017

Address for correspondence:
Luiz Fernando Costa Nascimento
Departamento de Energia, Universidade Estadual Paulista (UNESP)
Av. Ariberto Pereira da Cunha, 333
Guaratinguetá (SP) — Brasil
CEP 12516-410
Tel. (+55 12) 3123-2161
E-mail: luiz.nascimento@pq.cnpq.br

DOI: 10.1590/1516-3180.2017.0203290817

Cross-sectional study on the association between frailty and violence against community-dwelling elderly people in Brazil

Mariane Santos Belisário[I], Flavia Aparecida Dias[II], Maycon Sousa Pegorari[III], Mariana Mapelli de Paiva[IV], Pollyana Cristina dos Santos Ferreira[V], Fabrício Anibal Corradini[VI], Darlene Mara dos Santos Tavares[VII]

Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil

[I]Undergraduate Student, Nursing Course, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil.

[II]MSc. Doctoral Student, Postgraduate Course on Healthcare, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil.

[III]MSc. Physiotherapist and Assistant Professor, Physiotherapy Course, Universidade Federal do Amapá (UNIFAP), Macapá (AP) Brazil.

[IV]MSc. Nurse and Assistant Professor, Technical Nursing Course, Instituto Federal de Educação Ciência e Tecnologia do Norte de Minas Gerais (IFNMG), Almenara (MG), Brazil.

[V]MSc. Doctoral Student, Postgraduate Course on Healthcare, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil.

[VI]MD. Adjunct Professor, Department of Geography, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil.

[VII]MD, PhD. Associate Professor, Undergraduate Nursing Program, Department of Nursing Education and Community Health, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brazil.

KEY WORDS:
Elderly.
Frail elderly.
Violence.
Geographic information systems.
Spatial analysis.

ABSTRACT

BACKGROUND: The physical, emotional and cognitive limitations that may be present in the aging process, coupled with family unpreparedness, may lead to greater dependence among the elderly. This favors development of frailty syndrome and greater levels of violence against the elderly. The objective here was to analyze the association between violence against the elderly and frailty; and the geographic distribution of violence against the elderly according to the presence of frailty syndrome.

DESIGN AND SETTING: Cross-sectional study on 705 community-dwelling elderly people in Uberaba (MG), Brazil.

METHODS: The Fried frailty phenotype and conflict tactics scale were used. Data were analyzed using descriptive statistics, the chi-square test and a logistic regression model. The intensity of the events and the relationship between clusters of violence and frailty status were assessed by means of kernel estimation.

RESULTS: The adjusted analysis indicated that pre-frailty and frailty were associated with physical and verbal aggression (odds ratio, OR = 1.51; 95% confidence interval, CI: 1.04-2.19; OR = 2.12; 95% CI: 1.29-3.47), frailty was associated with physical aggression (OR = 2.48; 95% CI: 1.25-4.94) and pre-frailty and frailty were associated with verbal aggression (OR = 1.48; 95% CI: 1.03-2.15; OR = 2.15; 95% CI: 1.31-3.52), respectively. Regardless of frailty status and its relationship with violence, clusters of occurrences were larger in similar regions in the southeastern part of the municipality; but superimposition of overlays relating to aggression showed that for frail individuals the clusters were smaller than for non-frail and pre-frail individuals.

CONCLUSIONS: The condition of frailty was associated with greater chances of violence against the elderly.

INTRODUCTION

Amid the expansion of longevity, propitiated through advances in medicine and improvements in living standards, elderly people have been experiencing new situations that are considered adverse, such as increasing numbers of cases of violence against them.[1] Through the aging process, elderly people may become more susceptible to physical, emotional or cognitive limitations, which may lead to greater dependence.[2] This, together with family unpreparedness, low socioeconomic status and histories of violence among relatives, may contribute towards occurrences of violence against them in this phase of life.[3]

The World Health Organization has adopted the definition of violence against the elderly proposed by the International Network for the Prevention of Elderly Abuse (INPEA). This definition states that such violence is "an act (single or repeated) or omission that causes harm or distress and which occurs in any relationship in which there is an expectation of confidence".[4]

A multicenter study conducted among elderly people in different countries showed that 0.85% of the sample reported physical violence and 14.82% psychological violence. Female gender, low education levels, low income levels, multi-family living arrangements and lack of support from the partner, children and family were associated with cases of domestic violence, especially psychological violence.[5]

In Brazil, a review of the literature found that the prevalence of violence against the elderly ranged from 3.2% to 20.8%, depending on the cases reported and the region where each study was conducted. The types of event reported included psychological and physical violence, along with robbery. However, attention was drawn to the small number of studies conducted in this country on this subject, especially with regard to population-based studies, thus showing that there is a need to increase knowledge in this field.[6]

In this context, frailty among the elderly can be highlighted. This may lead to greater susceptibility to the risk of violence, which can be correlated with the level of functional dependence. This dependence increases the burden on caregivers who live in the same home, which may compromise the quality of care and interfere in family relationships.[7]

Another review of the literature[8] identified the prevalence of frailty syndrome among the elderly, finding a range from 6.9% to 39.1%. This range of results was ascribed to differences between countries and between the types of places evaluated (in the community or in hospitals, healthcare units or long-stay institutions), along with the instruments used.[8]

Considering these data, it is important to identify cases of risk of violence against the elderly that are related to the presence of frailty syndrome. To do so, tools such as georeferencing constitute an important technological resource that can contribute towards ascertaining the dimensions of a particular problem, in terms of where people affected by the problem are living, within a defined geographical area. These data can contribute towards better organization of care services, through planning of healthcare actions and decision-making that are directed towards the target public.[9]

OBJECTIVE

Based on the above, and considering the lack of studies evaluating maltreatment and/or violence against the elderly in the scientific literature, in relation to frailty syndrome, the objectives of the present study were to verify the association between violence against the elderly and frailty syndrome and to conduct a geographic analysis on violence against the elderly according to the presence of frailty syndrome.

METHODS

Study design, population and ethics

This was a household-based analytical and observational cross-sectional survey, developed among elderly residents in the urban area of the municipality of Uberaba (MG), Brazil. The sample size calculation used a prevalence of violence of 40%,[10] an accuracy of 3.5% and a 95% confidence interval for a finite population of 36,703 elderly people, and the sample size thus determined was 738 individuals. A sampling loss of 20% was taken into consideration, and it was decided that the maximum number of interviews to be attempted would be 923.

To select the elderly subjects, a multistage cluster sampling technique was used. In the first stage, an arbitrary draw of 50% of the census tracts of the municipality of Uberaba was carried out by means of systematic sampling. The sample interval (SI) was calculated by using the following formula: SI = total number of census tracts/number of census tracts selected. In the second stage, the number of elderly people to be interviewed according to the sample calculation (n = 738), was divided by the number of census tracts in the municipality (204). This proportion was approximated to four elderly people per census tract, in order to obtain an approximately similar number within each census tract.

The inclusion criteria were that the subjects needed to: be aged 60 or older; live in the urban area; have no cognitive impairment; be able to walk, for which use of a walking aid was allowed (walking stick, crutch or Zimmer frame); and agree to participate in the study through signing a free and informed consent statement. The following were considered to be exclusion criteria and losses: failure to find the elderly individual, after three attempts by the interviewer; being hospitalized; neurological diseases that made evaluations impossible; failure to complete all the tests for frailty; and occurrence of census tracts without elderly people or in which the number of elderly people required was not reached. Thus, 705 elderly people were interviewed. Data were collected from January to April 2014, in the respective homes of these elderly individuals, on a single occasion, through a direct interview.

This study was approved by the Ethics Committee for Research on Human Beings of the Federal University of the Triângulo Mineiro through report no. 573.833. The interviews were conducted only after the interviewees had given their consent through signing a free and informed consent statement.

Measurements

Initially, a cognitive assessment using the Mini-Mental State Examination (MMSE) was conducted. The cutoff point for cognitive decline took into consideration the respondents' educational level and was taken to be 13 points if the subject was illiterate, 18 points or less if the subject had attended school for between one and 11 years and 26 points if the subject had had more than 11 years of education.[11] An structured survey was used to characterize socioeconomic, clinical and health data. In addition, functional incapacity was measured using the Katz[12] and Lawton-Brody[13] questionnaires for basic activities of daily living (BADL) and instrumental activities of daily living (IADL), respectively.

Frailty syndrome was verified using the five items that were proposed by Fried et al.[14] for describing the components of the frailty phenotype, as follows:

1. Unintentional weight loss, assessed by the question: "In the past year, did you unintentionally lose more than 4.5 kg (i.e. without diet or exercise)?";
2. Diminished muscle strength, which was verified through handgrip strength using a manual hydraulic dynamometer (SAEHAN model). Three measurements expressed in kilogram-force (kgf) were obtained, with one-minute intervals between them. The mean value of the three measurements was used and the cutoff points proposed by Fried et al. were used;[14]

3. Self-reported exhaustion and/or fatigue: measured by means of two questions on the Brazilian version of the Center for Epidemiological Studies depression scale (CES-D): item 7 ("I felt everything I did was an effort") and item 20 ("I could not get going"). The elderly subjects who scored two or three in either of these questions fulfilled the frailty criteria for this item;[15]
4. Walking slowness, in which the time (in seconds) that was taken to walk a distance of 4.6 m was assessed. Three measurements expressed in seconds were made, and the mean value was used. The cutoff points used were as proposed by Fried et al.;[14]
5. Low physical activity level, as assessed using the International Physical Activity Questionnaire (long version), with adaptation for elderly people.[16] The classification used for this component was that elderly people who spent 150 minutes or more per week doing physical activities were considered active, while those who spent zero to 149 minutes per week doing physical activity were considered inactive.

Elderly subjects with three or more of the above items were classified as frail; those with one or two items were classified as pre-frail; and those for whom all the tests were negative were considered to be robust or non-frail.[14]

Violence was assessed using the translated and validated Brazilian version of the conflict tactics scale.[17] This instrument is composed of 19 questions encompassing negotiation, psychological aggression, physical assault, sexual coercion and injury. The score range is from 0 to 19. Psychological or physical violence was considered to have occurred when the elderly subjects reported that they had been the victims of at least one item on the verbal aggression subscale (questions 4-9) and physical aggression subscale (questions 10-19).[17]

The variables studied were: socioeconomic data; number of diseases; number of medications; BADL and IADL dependency; frailty syndrome; and physical and verbal aggression.

Statistical analysis

The data were analyzed through the Statistical Package for the Social Sciences (SPSS) software, version 17.0. To characterize the population, the statistical analysis was performed using the absolute and percentage frequency distribution for the categorical variables.

To ascertain associations between violence and socioeconomic, clinical and health variables, the chi-square and Student t tests were used. Logistic regression was used to examine the condition of frailty that was associated with physical and psychological violence, with adjustments for age, sex, number of diseases and number of medications. The significance level (α) was set at 5%.

For the spatial analysis, the MapInfo Professional software, version 9.5, and the TerraView software, version 3.3.1, were used. A georeferenced database was built to spatialize the data, by using the Geographic Information System (GIS) tools through the ArcGis 10.2 application. The intensities of the events and the relationships of clusters of violence with frailty status (number of events per unit area) were assessed through kernel estimates, with an adaptive algorithm for the radius of the quartic function. The maps generated for each event were subjected to a reclassification process, followed by multicriterion analysis with weighted overlays, with the aim of ascertaining whether the different events overlapped and what their common occurrence area was. It should be noted that all products generated were adjusted to the same horizontal datum (SIRGAS 2000) and that the Universal Transverse Mercator (UTM) coordinate system was used.

RESULTS

Among the interviewees (n = 705), the highest percentages were female (66.8%), in the age group 60 ├70 years (43.1%) were married (42%), had a monthly income of one minimum monthly wage (45%), had had 4 ├8 years of schooling (36.5%) and lived with a companion (78.9%). Regarding violence, 20.9% of the elderly subjects reported that they had suffered verbal aggression, 7.9% physical aggression and 21.13% physical and/or verbal aggression. Regarding their condition of frailty, it was found that 15.9% (n = 112) were frail, 52.2% (n = 368) were pre-frail and 31.9% (n = 225) were non-frail.

Associations between the following variables and types of violence were observed: individual monthly income of one minimum wage (physical aggression); living with another person and IADL dependency (physical and/or verbal aggression and verbal aggression); and a large number of diseases (physical and/or verbal aggression, physical aggression and verbal aggression). Regardless of the type of aggression, the highest proportion of the victims comprised pre-frail elderly people. However, the proportion of frail elderly people who reported having suffered physical and/or verbal aggression, physical aggression and verbal aggression was higher than the proportion of frail elderly people who reported that they had not suffered any aggression, as shown in **Table 1**.

The adjusted analysis indicated that the conditions of pre-frailty and frailty were both associated with higher odds ratios for physical and/or verbal aggression, while the condition of frailty alone was associated with physical aggression and the conditions of pre-frailty and frailty were both associated with verbal aggression (**Table 2**).

The geospatial analysis showed that the non-frail elderly people were present in several regions of the municipality (**Figure 1A**). Superimposition of overlays relating to verbal aggression (**Figure 1B**) and physical aggression (**Figure 1C**) showed that non-frail elderly people suffering from these problems were concentrated in the southeastern region of the municipality, but that non-frail elderly

Table 1. Socioeconomic, clinical and health variables according to distribution of types of violence. Uberaba (MG), Brazil, 2014

Variables	Physical and/or verbal aggression		Physical aggression		Verbal aggression	
	Yes	No	Yes	No	Yes	No
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex						
Male	44 (29.5)	190 (34.2)	19 (33.9)	215 (33.1)	43 (29.1)	191 (34.3)
Female	105 (70.5)	366 (65.8)	37 (66.1)	434 (66.9)	105 (70.9)	366 (65.7)
P*	0.285		0.903		0.229	
Age range (years)						
60 ⊢70	70 (47.0)	243 (42.1)	29 (51.8)	275 (42.4)	69 (46.6)	235 (42.2)
70 ⊢80	53 (35.6)	204 (36.7)	19 (33.9)	238 (36.7)	53 (35.8)	204 (36.6)
80 or over	26 (17.4)	118 (21.2)	8 (14.3)	136 (21.0)	26 (17.6)	118 (21.2)
P*	0.470		0.318		0.521	
Length of schooling (years)						
Illiterates	25 (16.8)	110 (19.8)	8 (14.3)	127 (19.6)	25 (16.9)	110 (19.7)
1 ⊢4	37 (24.8)	129 (23.2)	16 (28.6)	150 (23.1)	37 (25.0)	129 (23.2)
4 ⊢8	58 (38.9)	199 (35.8)	26 (46.4)	231 (35.6)	57 (38.5)	200 (35.9)
8	14 (9.4)	35 (6.3)	3 (5.4)	46 (7.1)	14 (9.5)	35 (6.3)
9 or more	15 (10.1)	83 (14.9)	3 (5.4)	95 (14.6)	15 (10.1)	83 (14.9)
P*	0.328		0.166		0.343	
Marital Status						
With a companion	12 (8.1)	41 (7.4)	4 (7.1)	49 (7.6)	12 (8.1)	41 (7.4)
Without a companion	137 (91.9)	515 (92.6)	52 (92.9)	600 (92.4)	136 (91.9)	516 (92.6)
P*	0.780		0.585		0.759	
Monthly income (in minimum wages)						
No income	10 (6.7)	53 (9.5)	3 (5.4)	60 (9.2)	10 (6.8)	53 (9.5)
< 1	7 (4.7)	9 (1.6)	6 (10.7)	10 (1.5)	7 (4.7)	9 (1.6)
1	71 (47.7)	246 (44.2)	27 (48.2)	290 (44.7)	70 (47.3)	247 (44.3)
1 ⊢3	49 (32.9)	182 (32.7)	20 (35.7)	211 (32.5)	49 (33.1)	182 (32.7)
3 ⊢5	8 (5.4)	41 (7.4)	0 (0)	49 (7.6)	8 (5.4)	41 (7.4)
> 5	4 (2.7)	25 (4.5)	0 (0)	29 (4.5)	4 (2.7)	25 (4.5)
P*	0.163		**< 0.001**		0.169	
Living arrangements						
Alone	20 (13.4)	129 (23.2)	8 (14.3)	141 (21.7)	20 (13.5)	129 (23.2)
Not alone	129 (86.6)	427 (76.8)	48 (85.7)	508 (78.3)	128 (86.5)	428 (76.8)
P*	**0.009**		0.191		**0.011**	
Number of diseases (mean ± SD)	6.62 ± 3.79	5.47 ± 3.36	7.39 ± 3.92	5.57 ± 3.41	6.61 ± 3.8	5.48 ± 3.36
P†	**< 0.001**		**< 0.001**		**0.001**	
Number of medications (mean ± SD)	3.53 ± 0.520	3.36 ± 2.75	3.57 ± 2.89	3.38 ± 2.76	3.51 ± 2.88	3.37 ± 2.75
P†	0.520		0.631		0.576	
Dependency in BADL (mean ± SD)	0.03 ± 0.21	0.02 ± 0.15	0.03 ± 0.18	0.02 ± 0.16	0.03 ± 0.21	0.02 ± 0.15
P†	0.448		0.597		0.439	
Dependency in IADL (mean ± SD)	1.05 ± 1.44	0.72 ± 1.25	03.91 ± 1.10	0.77 ± 1.32	1.04 ± 1.45	0.72 ± 1.25
P†	**0.012**		0.461		**0.013**	
Frailty						
Non-frail	45 (30.2)	180 (32.4)	14 (25.0)	211 (32.5)	44 (29.7)	181 (32.5)
Pre-frail	67 (45.0)	301 (54.1)	25 (44.6)	343 (52.9)	67 (45.3)	301 (54.0)
Frail	37 (24.8)	75 (13.5)	17 (30.4)	95 (14.6)	37 (25.0)	75 (13.5)
P*	**0.003**		**0.008**		**0.003**	

P < 0.05; *chi-square test; †Student t test; BADL = basic activities of daily living; IADL = instrumental activities of daily living; SD = standard deviation.

Table 2. Logistic regression model according to the classification of violence according to frailty levels. Uberaba (MG), Brazil, 2014

Frailty levels	Physical and/or verbal aggression			Physical aggression			Verbal aggression		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Non-frail		1			1			1	
Pre-frail									
Non-adjusted	1.44	1.01-2.08	**0.047**	1.39	0.80-2.41	0.240	1.42	0.99-2.05	0.058
Adjusted	1.51	1.04-2.19	**0.029**	1.45	0.83-2.55	0.191	1.48	1.03-2.15	**0.036**
Frail									
Non-adjusted	2.12	1.36-3.30	**0.001**	2.54	1.38-4.67	**0.003**	2.14	1.37-3.34	**0.001**
Adjusted	2.12	1.29-3.47	**0.003**	2.48	1.25-4.94	**0.010**	2.15	1.31-3.52	**0.002**

OR = odds ratio; 95% CI = 95% confidence interval; P < 0.05; 1 = reference category; adjustments were made for age, sex, number of diseases and number of medications.

people suffering from physical aggression presented at lower density than those suffering from verbal aggression. The overlay showing physical/verbal aggression (**Figure 1D**) in relation to areas with non-frail elderly people demonstrated that the individuals suffering from physical/verbal aggression were concentrated in the southeastern region of the municipality.

Pre-frail elderly people were concentrated in the southeastern region and close to the central region (**Figure 2A**). Superimposition of overlays relating to verbal aggression (**Figure 2B)** and physical aggression (**Figure 2C**) showed that the region with pre-frail elderly people suffering from these problems was the southeastern region. The areas shown by the overlay relating

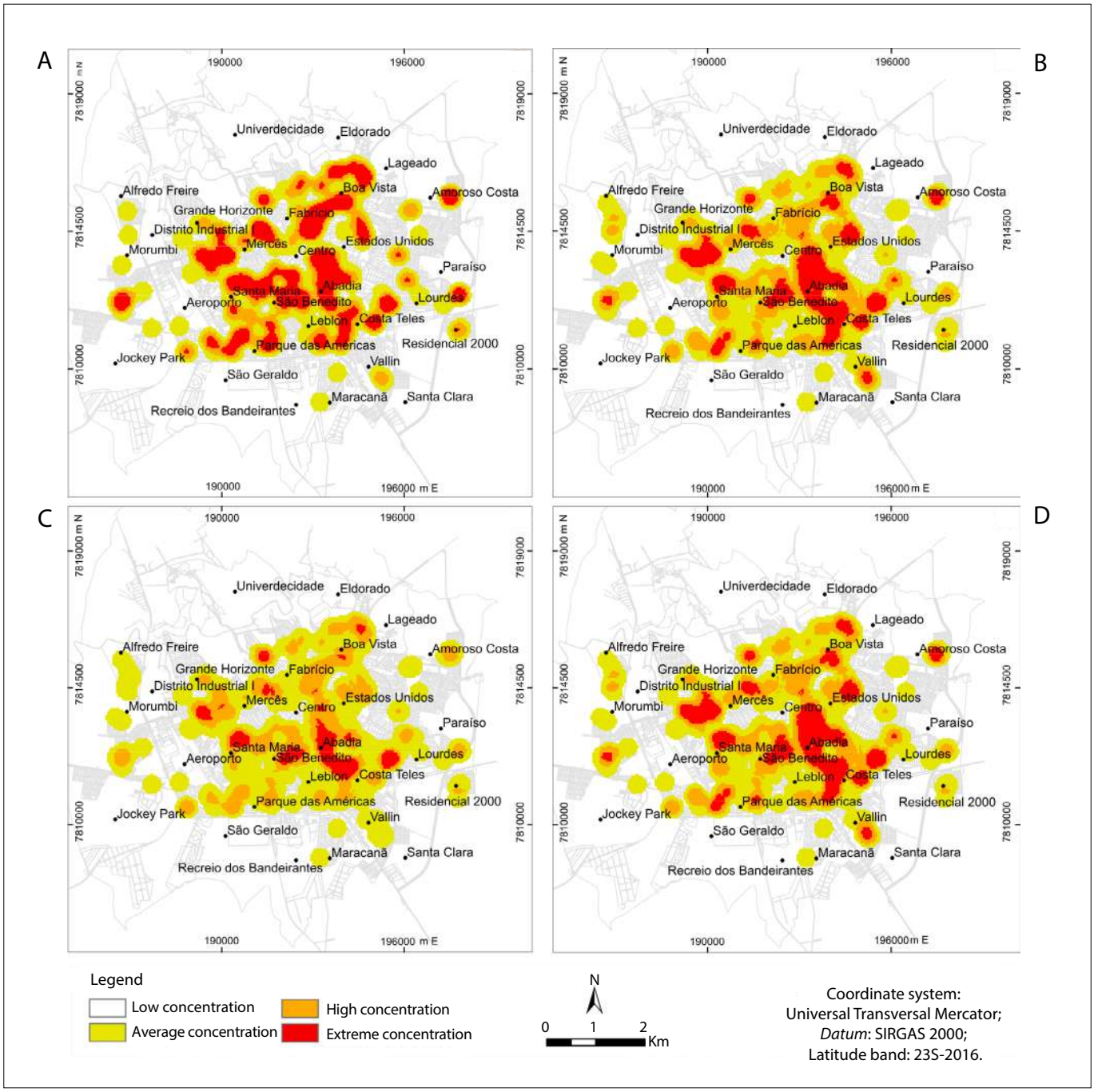


Figure 1A. Map of where non-frail elderly people were living; **1B**. With overlay regarding verbal aggression; **1C**. With overlay regarding physical aggression; **1D**. With overlay regarding verbal/physical aggression. Uberaba (MG), Brazil, 2014. Concentration data relate to qualitative information.

to physical/verbal aggression coincided with the southeastern region, but were smaller (**Figure 2D**).

Frail elderly people were concentrated mainly in the southern region of the municipality (**Figure 3A**). Superimposition of overlays relating to verbal aggression (**Figure 3B**) and physical aggression (**Figure 3C**) showed that the southeastern region presented the largest concentration of frail elderly people. Overlaying of physical/verbal aggression on areas with frail elderly people showed that these areas coincided with the southeastern region, but were smaller than the area in which individuals suffered from verbal aggression (**Figure 3D**).

DISCUSSION

This study demonstrated that conditions of frailty were associated with higher odds ratios for physical and/or verbal aggression, physical aggression and verbal aggression. Regardless of

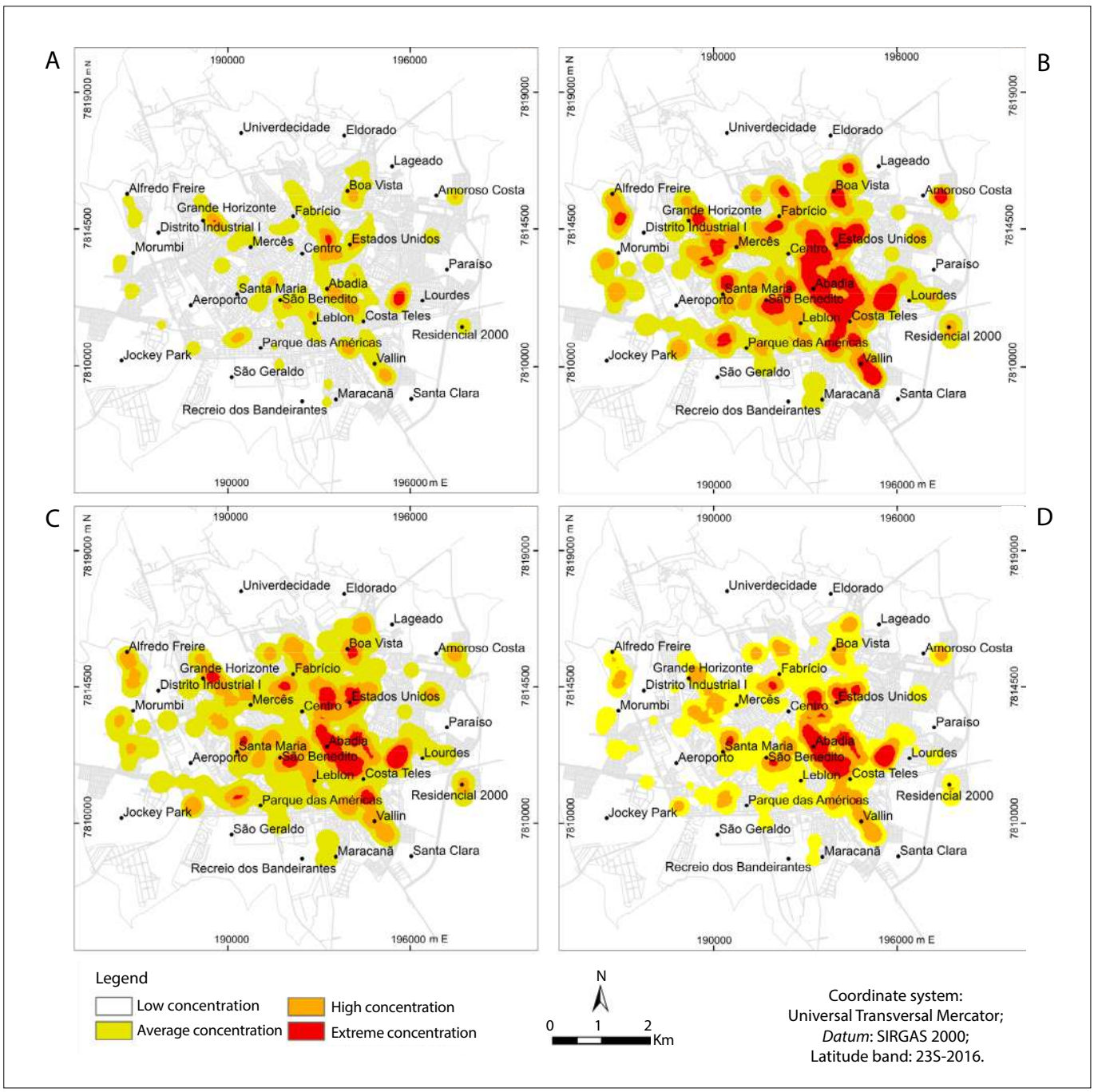


Figure 2A. Map of where pre-frail elderly people were living; **2B**. With overlay regarding verbal aggression; **2C**. With overlay regarding physical aggression; **2D**. With overlay regarding verbal/physical aggression. Uberaba (MG), Brazil, 2014. Concentration data relate to qualitative information.

frailty status and its relationship with violence, clusters of occurrences were larger in the southeastern part of the municipality; but for frail individuals the clusters were lower than for non-frail and pre-frail individuals.

In relation to the sociodemographic data, the present study showed that the elderly people investigated here followed the trend observed in other studies. i.e. the subjects of the present study were predominantly female and younger elderly people who were married, had had little schooling and were living with other people.[5,18]

Regarding the types of violence, a Brazilian study[19] and a multicenter study[5] showed different prevalences of physical and psychological violence. This may have been related to the definitions for violence that were used, along with social differences.[20]

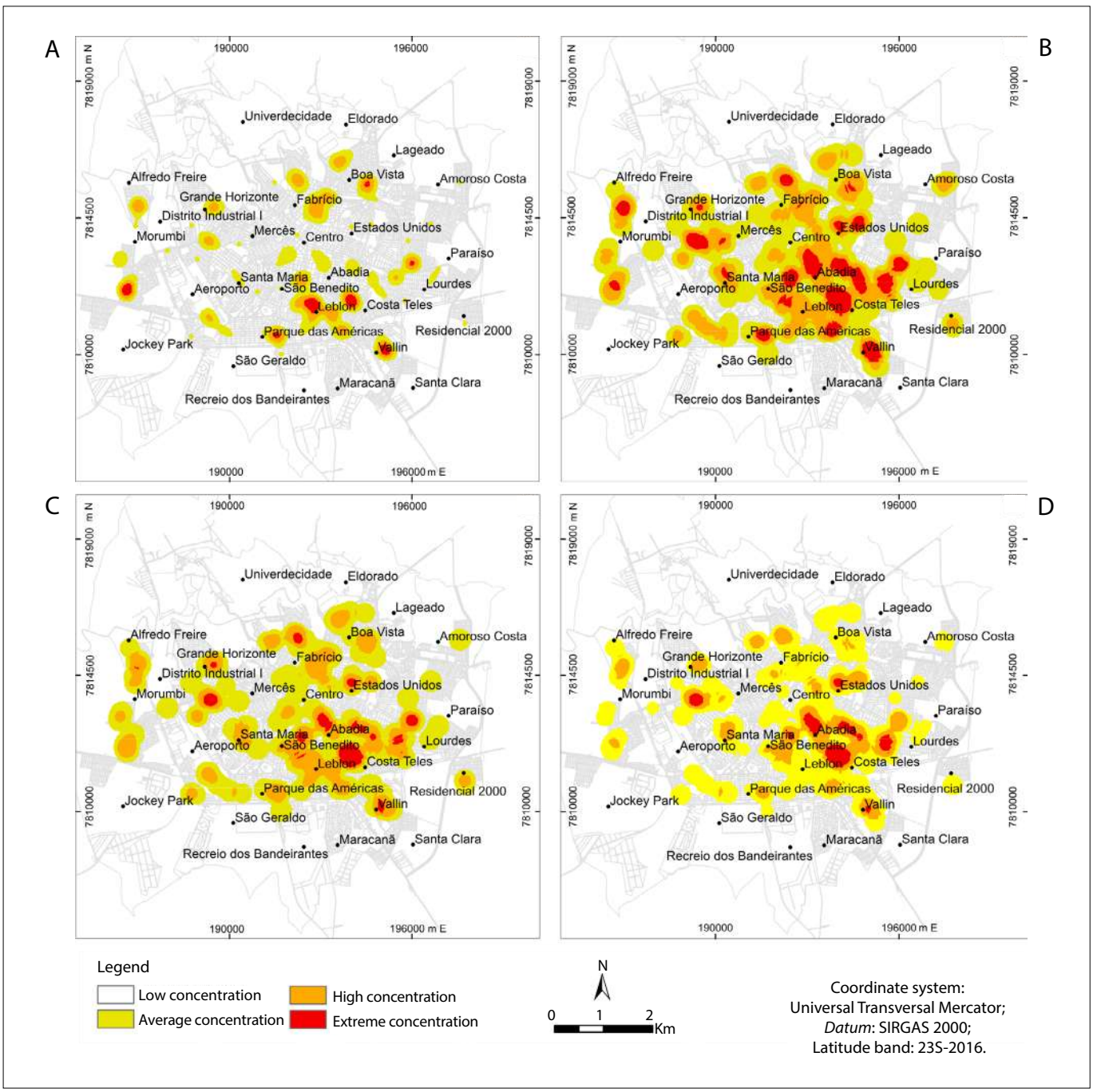


Figure 3A. Map of where frail elderly people were living; **1B**. With overlay regarding verbal aggression; **1C**. With overlay regarding physical aggression; **1D**. With overlay regarding verbal/physical aggression. Uberaba (MG), Brazil, 2014. Concentration data relate to qualitative information.

A survey conducted in the city of Campinas, state of São Paulo, Brazil,[21] showed lower prevalence than the present study, such that 9.1% of the community-dwelling elderly people were frail, while the percentage of pre-frail elderly people was similar (51.8%). However, a systematic review with meta-analysis revealed higher prevalence of frail conditions (19.1%) in countries in the Latin American and Caribbean region.[22]

The results regarding socioeconomic data and occurrence of violence were consistent with those from other studies, for the variables of sex,[19] age group,[23] marital status,[24] schooling[19,23] and income.[5] The sociodemographic context that was identified suggests that the issue of violence remains linked to the most vulnerable groups, i.e. women and individuals of lower social and economic levels. With regard to age group, younger adults are assumed to have a lower degree of dependence because their younger age makes it easier to seek help and to identify more cases of violence.[25] On the other hand, in relation to marital status, although this was not investigated in the present study, married women might present some dependence on their spouses, which might increase the possibility of becoming victims of their partners.[25]

The results relating to the proportion of frail elderly people among the elderly people who reported occurrences of aggression, and the association between the condition of frailty and occurrences of physical and/or verbal aggression, physical aggression and verbal aggression, are corroborated by the findings from a systematic review that showed that worse health conditions or frailty were risk factors for abuse among community-dwelling elderly people.[26]

Other studies have mentioned the expression "frailty", although without any established conceptual and operational definition, and have correlated this with neglect of care and signs of abandonment among hospitalized elderly people;[27] or with specific components of vulnerability to abuse among elderly people, with regard to disability and mortality rates.[28] One point that needs to be mentioned is that the Brazilian Ministry of Health's recommended definition for frail elderly people or for individuals in a frail condition includes scenarios of living with situations of domestic violence, among other situations envisaged.[29]

Thus, identification of conditions of frailty and care for frail elderly people should include directed and expanded investigation of whether cases and/or situations of violence might exist. In addition, screening and/or early diagnosis may favor implementation of preventive measures aimed at addressing frailty syndrome and occurrences of violence against elderly people.

In the spatial analysis, regardless of frailty status and its relationship with violence, the clusters of elderly were largest in the same region of the southeast of the municipality. This suggests that other factors, possibly relating to space, may have interfered with these variables. It should be noted that the areas highlighted present concentrations of people with low incomes and have lower percentages of literate people than elsewhere.[30]

Less schooling and low income characterized the elderly victims of violence.[31] Individuals with higher levels of education are likely to suffer less violence, since they have a minimum critical level that enables them to reduce or avoid abuse.[32] In addition, groups with higher education seek other sectors, such as medical and legal services, to solve the problem.[33] Thus, during professional care, it is necessary to consider the level of schooling of elderly patients, in order to facilitate understanding of the guidelines for the rights of elderly people.

In a bibliographical survey on the social determinants of violence, in relation to the health of vulnerable populations in Latin America, it was found that, among other factors, excess urban violence is related to income inequality.[34] Thus, in view of the complexity of violence, there is a need for a broader view that considers its interdependence among individual, relational and cultural determinants.[35]

It is noteworthy that we were unable to find any other spatial analysis studies correlating conditions of frailty with violence among elderly people, which thus limits the possibilities for discussing this. On the other hand, we found some surveys on violence against women, and these showed that there was greatest occurrence in geographical spaces with less favored social conditions or in situations of greater social inequality.[36,37]

Hence, mapping of the areas at greater risk can direct the attention of the public authorities towards actions focusing on geographical spaces identified through this process.[36] Identification of places where there are concentrations of elderly people in conditions of frailty/pre-frailty who suffer violence can guide healthcare provision at the primary care level.

There is a need to prepare professionals at this level of care to meet this demand. Professional and institutional supervision services need to be offered by public managers, in order to improve the team's ability to listen to patients' complaints and encourage greater professional participation in making decisions and connecting services together.[35]

In this regard, it should be pointed out that there need to be links between the judicial, safety, health, social and educational support systems, along with community awareness campaigns focusing on the different types of violence that the elderly are exposed to.[31]

The limitations of the present study included its cross-sectional design, in which the data were collected at a single time. This made it impossible to ascertain the causal relationship between the variables. Nonetheless, despite the characteristics of the methodology used, the results from this study add knowledge to this topic. Variables that have been little explored in the scientific literature, namely frailty and violence against the elderly were analyzed here. Thus, the findings from the present study add support

for proposals for preventive interventions and behaviors directed towards addressing the conditions of violence against the elderly and frailty among the elderly.

CONCLUSION

The proportion of frail elderly people who reported occurrences of aggression was higher than the proportion of them who did not report such occurrences. The condition of frailty was associated with higher odds ratios for physical and/or verbal aggression, physical aggression and verbal aggression. Regardless of frailty status and its relationship with violence, the clusters of elderly people were larger in similar regions of the southeastern part of the municipality.

REFERENCES

1. Sales DS, Parente F, Silva MJ, et al. A violência contra o idoso na visão do agente comunitário de saúde [The violence against the elderly from the community health worker's view]. Estud Interdiscip Envelhec. 2014;19(1):63-77.
2. Machado JC, Rodrigues VP, Vilela ABA, et al. Violência intrafamiliar e as estratégias de atuação da equipe de Saúde da Família [Intrafamily violence and actions strategies of the Family Health team]. Saúde Soc. 2014;23(3):828-40.
3. Oliveira MLC, Gomes ACG, Amaral CPM, Santos LB. Características dos idosos vítimas de violência doméstica no Distrito Federal [Characteristics of elderly people victim of domestic violence in the Federal District, Brazil]. Rev Bras Geriatr Gerontol. 2012;15(3):555-66.
4. World Health Organization. The Toronto Declaration on the Global Prevention of Elder Abuse. International Network for the Prevention of Elder Abuse. Geneva World Health Organization; 2002. Available from: http://www.who.int/ageing/projects/elder_abuse/alc_toronto_declaration_en.pdf. Accessed in 2017 (Sep 14).
5. Guedes DT, Curcio CL, Llano BA, Zunzunegui MV, Guerra R. La brecha de género en violencia doméstica en adultos mayores en América Latina: el Estudio IMIAS [The gender gap in domestic violence in older adults in Latin America: the IMIAS Study]. Rev Panam Salud Pública. 2015;37(4/5):293-300.
6. Santana IO, Vasconcelos DC, Coutinho MPL. Prevalência da violência contra o idoso no Brasil: revisão analítica [Prevalence of violence against elderly in the Brazil: analytic review]. Arq Bras Psicol (Rio J 2003). 2016;68(1):126-39.
7. Stackfleth R, Diniz MA, Fhon JRS, et al. Sobrecarga de trabalho em cuidadores de idosos fragilizados que vivem no domicílio [Burden of work in caregivers of frail elders living at home]. Acta Paul Enferm. 2012;25(5):768-74.
8. Lana LD, Schneider RH. Síndrome de fragilidade no idoso: uma revisão narrativa [The frailty syndrome in elderly: a narrative review]. Rev Bras Geriatr Gerontol. 2014;17(3):673-80.
9. Ribeiro MA, Albuquerque IMN, Paiva GM, et al. Georreferenciamento: ferramenta de análise do sistema de saúde de Sobral – Ceará [Georeferencing: analysis tool for the health system in Sobral, Ceará]. Sanare. 2014;13(2):63-9. Available from: https://sanare.emnuvens.com.br/sanare/article/view/583/316. Accessed in 2017 (Sep 14).
10. Espíndola CR, Blay SL. Prevalência de maus-tratos na terceira idade: revisão sistemática [Prevalence of elder abuse: a systematic review]. Rev Saúde Pública. 2007;41(2):301-6.
11. Bertolucci PHF, Brucki SMD, Campacci SR, Juliano Y. O mini-exame do estado mental em uma população geral: impacto da escolaridade [The mini-mental state examination in a general population: impact of educational status]. Arq Neuropsiquiatr. 1994;52(1):1-7.
12. Lino VT, Pereira SR, Camacho LA, Ribeiro Filho ST, Buksman S. Adaptação transcultural da Escala de Independência em Atividades de Vida Diária (Escala de Katz) [Cross-cultural adaptation of the Independence in Activities of Daily Living Index (Katz Index)]. Cad Saúde Pública. 2008;24(1):103-12.
13. Santos RL, Virtuoso Júnior JS. Confiabilidade da versão brasileira da escala de atividades instrumentais da vida diária [Reliability of the Brazilian version of the Scale of Instrumental Activities of Daily Living]. Revista Brasileira em Promoção da Saúde. 2008;21(4):290-6. Available from: http://hp.unifor.br/pdfs_notitia/2974.pdf. Accessed in 2017 (Sep 14).
14. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
15. Batistoni SS, Neri AL, Cupertino AP. Validade da escala de depressão do Center for Epidemiological Studies entre idosos brasileiros [Validity of the Center for Epidemiological Studies Depression Scale among Brazilian elderly]. Rev Saúde Pública. 2007;41(4):598-605.
16. Benedetti TB, Mazo GZ, Barros MVG. Aplicação do Questionário Internacional de Atividades Físicas para avaliação do nível de atividades físicas de mulheres idosas: validade concorrente e reprodutibilidade teste-reteste [Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reproducibility]. Rev Bras Ciênc Mov. 2004;12(1):25-34.
17. Hasselmann MH, Reichenheim ME. Adaptação transcultural de versão em português da Conflict Tactics Scales Form R (CTS-1), usada para aferir violência no casal: equivalências semânticas e de mensuração [Cross-cultural adaptation of the Portuguese version of the Conflict Tactics Scales Form R (CTS-1) used to assess marital violence: semantic and measurement equivalence]. Cad Saúde Pública. 2003;19(4):1083-93.
18. Guedes DT, Alvarado BE, Philips SP, et al. Socioeconomic status, social relations and domestic violence (DV) against elderly people in Canada, Albania, Colombia and Brazil. Arch Gerontol Geriatr. 2015;60(3):492-500.
19. Mascarenhas MD, Andrade SS, das Neves AC, et al. Violência contra a pessoa idosa: análise das notificações realizadas no setor saúde – Brasil, 2010 [Violence against the elderly: analysis of the reports made in the health sector – Brazil, 2010]. Ciên Saúde Colet. 2012;17(9):2331-41.
20. Crome P, Moulias R, Sánchez-Castellano C, et al. Elder abuse in Finland, France, Spain and United Kingdom. European Geriatric Medicine. 2014;5(4):277-84. Available from: http://www.sciencedirect.com/science/article/pii/S187876491400103X. Accessed in 2017 (Sep 14).

21. Neri AL, Yassuda MS, Araújo LF, et al. Metodologia e perfil sociodemográfico, cognitivo e de fragilidade de idosos comunitários de sete cidades brasileiras: Estudo FIBRA [Methodology and social, demographic, cognitive, and frailty profiles of community-dwelling elderly from seven Brazilian cities: the FIBRA Study]. Cad Saúde Pública. 2013;29(4):778-92.
22. Da Mata FA, Pereira PP, Andrade KR, et al. Prevalence of Frailty in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(8):e0160019.
23. Aguiar MPC, Leite HA, Dias IM, Mattos MCT, Lima WR. Violência contra idosos: descrição de casos no Município de Aracaju, Sergipe, Brasil [Violence against the elderly: case description in the city of Aracaju, Sergipe, Brazil]. Esc Anna Nery Rev Enferm. 2015;19(2):343-9.
24. Abath MB, Leal MCC, Melo Filho DA. Fatores associados à violência doméstica contra a pessoa idosa [Factors associated with physical domestic violence in elderly victims]. Rev Bras Geriatr Gerontol. 2012;15(2):305-14.
25. Garbin CAS, Joaquim RC, Rovida TAS, Garbin AJI. Idosos vítimas de maus-tratos: cinco anos de análise documental [Elderly victims of abuse: a five year document analysis]. Rev Bras Geriatr Gerontol. 2016;19(1):87-94.
26. Johannesen M, LoGiudice D. Elder abuse: a systematic review of risk factors in community-dwelling elders. Age Ageing. 2013;42(3):292-8.
27. Cohen M. Research assessment of elder neglect and its risk factors in a hospital setting. Intern Med J. 2008;38(9):704-7.
28. Schofield MJ, Powers JR, Loxton D. Mortality and disability outcomes of self-reported elder abuse: a 12-year prospective investigation. J Am Geriatr Soc. 2013;61(5):679-85.
29. Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria nº 2.528 de 19 de outubro de 2006. Aprova a Política Nacional de Saúde da Pessoa Idosa. Diário Oficial da União, 142-5. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2006/prt2528_19_10_2006.html. Accessed in 2017 (Sep 14).
30. Ferreira RV, Bueno ACC. Atlas do município de Uberaba. Uberaba: Universidade Federal do Triângulo Mineiro/Laboratório de Cartografia e Geoprocessamento; 2014.
31. Gil AP, Santos AJ, Kislaya I, et al. Estudo sobre pessoas idosas vítimas de violência em Portugal: sociografia da ocorrência [A sociography of elderly victims of family violence in Portugal]. Cad Saúde Pública. 2015;31(6):1234-46.
32. Skirbekk V, James KS. Abuse against elderly in India--the role of education. BMC Public Health. 2014;14:336.
33. Sousa AKA, Nogueira DA, Gradim CVC. Perfil da violência doméstica e familiar contra a mulher em um município de Minas Gerais, Brasil [Profile of domestic violence against women and family in a city of Minas Gerais, Brazil]. Cad Saúde Colet (Rio J). 2013;21(4):425-31.
34. Hoefel MFL, Amate EM, Loiola AA, Carneiro FF. Determinantes sociais da violência na saúde de populações da América Latina [Social determinants of violence in the health of populations of Latin America]. Revista Eletrônica Gestão & Saúde. 2015;6(2):1786-804. Available from: http://periodicos.unb.br/index.php/rgs/article/view/22501/16098. Accessed in 2017 (Sep 14).
35. Wanderbroocke AC, Moré CL. Abordagem profissional da violência familiar contra o idoso em uma unidade básica de saúde [A professional approach to family violence against the elderly in a primary health clinic]. Cad Saúde Pública. 2013;29(12):2513-22.
36. Lucena KD, Silva AT, Moraes RM, Silva CC, Bezerra IM. Análise espacial da violência doméstica contra a mulher entre os anos de 2002 e 2005 em João Pessoa, Paraíba, Brasil [Spatial analysis of domestic violence against women from 2002 to 2005 in João Pessoa, Paraíba State, Brazil]. Cad Saúde Pública. 2012;28(6):1111-21.
37. Augusto AO, Lima VLA, Sena LX, et al. Mapeamento dos casos de violência contra a mulher na região metropolitana de Belém narrados pela mídia impressa do estado do Pará [Mapping cases of violence against in the metropolitan area of Belém narrated by printed media in state of Pará.]. Rev Para Med. 2015;29(2):23-32.

Sources of funding: Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG), under procedural number APQ -02035-14
Conflict of interest: None

Date of first submission: June 29, 2017
Last received: August 4, 2017
Accepted: August 29, 2017

Address for correspondence:
Darlene Mara dos Santos Tavares
Departamento de Enfermagem em Educação e Saúde Comunitária do Curso de Graduação em Enfermagem da Universidade Federal do Triangulo Mineiro (UFTM)
Av. Frei Paulino, 30
Abadia — Uberaba (MG) — Brasil
CEP 38025-180
Tel. (+55 34) 3700-6154
E-mail: darlene.tavares@uftm.edu.br

DOI: 10.1590/1516-3180.2017.0222290817

Prevalence of electrocardiographic abnormalities in primary care patients according to sex and age group. A retrospective observational study

Julia Pereira Afonso dos Santos[I], Antonio Luiz Pinho Ribeiro[II], Diomildo Andrade-Junior[III], Milena Soriano Marcolino[IV]

Department of Internal Medicine and Telehealth Network of Minas Gerais, University Hospital, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil

[I]Medical Student, Department of Internal Medicine, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil.
[II]MD, PhD. Full Professor, Department of Internal Medicine, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil.
[III]MD. Physician, Department of Internal Medicine, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil.
[IV]MD, MSc, PhD. Associate Professor, Department of Internal Medicine, Medical School, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil.

KEY WORDS:
Electrocardiography.
Sex.
Age groups.
Primary health care.

ABSTRACT

BACKGROUND: Knowledge of the prevalence of electrocardiographic abnormalities in a population is useful for interpreting the findings. The aim here was to assess the prevalence of electrocardiographic abnormalities and self-reported comorbidities and cardiovascular risk factors according to sex and age group among Brazilian primary care patients.

DESIGN AND SETTING: Observational retrospective study on consecutive primary care patients in 658 cities in the state of Minas Gerais, Brazil, whose digital electrocardiograms (ECGs) were sent for analysis to the team of the Telehealth Network of Minas Gerais (TNMG).

METHODS: All ECGs analyzed by the TNMG team in 2011 were included. Clinical data were self-reported and electrocardiographic abnormalities were stratified according to sex and age group.

RESULTS: A total of 264,324 patients underwent ECG examinations. Comorbidities and cardiovascular risk factors were more frequent among women, except for smoking. Atrial fibrillation and flutter, premature beats, intraventricular blocks, complete right bundle branch block and left ventricular hypertrophy were more frequent among men, and nonspecific ventricular repolarization abnormalities and complete left bundle branch block among women.

CONCLUSION: Electrocardiographic abnormalities were relatively common findings, even in the younger age groups. The prevalence of electrocardiographic abnormalities increased with age and was higher among men in all age groups, although women had higher frequency of self-reported comorbidities.

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide[1] and have a high socioeconomic impact.[2] The high mortality and morbidity associated with these diseases makes diagnosis and management of these conditions essential in clinical practice.

Electrocardiograms (ECGs) are important examinations for assessing cardiac disease. Prior knowledge of the prevalence of abnormalities in the population studied is useful for interpreting ECG findings.[3] Additionally, electrocardiographic abnormalities are independently associated with the incidence of coronary heart disease and with poor cardiac disease outcomes.[4]

The prevalence of electrocardiographic abnormalities varies with age and sex.[3,5,6] Recently, many studies have focused on the unique aspects of cardiac disease in women, in order to optimize its diagnosis and treatment.[4,7,8] In this regard, the present study may contribute to the literature on the subject through highlighting the differences in ECG findings between men and women in separate age groups, in a large sample of Brazilian primary care patients, and through discussing the particularities of female ECGs in relation to male ones.

OBJECTIVE

The aim of this study was to analyze the prevalences of self-reported comorbidities and electrocardiographic abnormalities according to age and sex among Brazilian primary care patients. Some specific aspects of women's ECGs in relation to men's ones are also discussed.

METHODS

This retrospective observational study included all ECGs that were recorded in primary care units and then analyzed by cardiologists of the Telehealth Network of Minas Gerais (TNMG),

a Brazilian large-scale public telehealth service, from January 1 to December 31, 2011. During this period, the service provided support to primary care practitioners in 658 municipalities in the state of Minas Gerais, among which 85% have fewer than 14,000 inhabitants. It performed teleconsultations and remote interpretation of diagnostic tests, including ECG analysis.[9]

Digital 12-lead electrocardiograms were produced using tele-electrocardiograph machines made by Tecnologia Eletrônica Brasileira (TEB; São Paulo, Brazil) or Micromed Biotechnology (Brasília, Brazil) and were sent over the internet to an analysis center, from which the examinations were immediately forwarded to a team of cardiologists, who analyzed the ECGs using standardized criteria.[10] The team of cardiologists was composed of ten cardiologists who had been trained and were experienced in ECG analysis. Their ECG analyses were also subject to periodic auditing and feedback.[9] Only one individual reviewed each ECG.

The clinical data were self-reported and were gathered immediately before the patients were subjected to the ECG exam. A standard questionnaire was used, which sought data including age, sex, medications in use, comorbidities (hypertension, diabetes, obesity, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease and coronary artery disease), prior acute myocardial infarction, smoking and family history of coronary heart disease.

For the purpose of this study, all consecutive ECGs from January 1, 2011, to December 31, 2011, were analyzed. Electrocardiograms with technical issues such as interference or errors in the placement of electrodes were excluded. The proportion of atrial flutter was considered along with the proportion of atrial fibrillation, as has also been done in other epidemiological studies.[11] The prevalence of electrocardiographic abnormalities was evaluated and stratified according to sex and age groups. The age groups encompassed every two decades of life: from 0 to 19.9 years of age; 20 to 39.9; 40 to 59.9; 60 to 79.9; and greater than or equal to 80 years. Rankings of the most common abnormalities according to age group and sex were elaborated and a table of the final ranking according to sex and age group was constructed.

The IBM SPSS statistics software for Windows version 20.0 (2011 release; IBM Corporation, Armonk, NY, USA) was used for the statistical analyses. Categorical variables were reported as counts and percentages; continuous variables were reported as means and standard deviations (SD) or medians with interquartile range (IQR), as appropriate. This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

RESULTS

Over the course of this study, ECG recordings from 264,324 primary care patients were analyzed by the TNMG cardiology team; 58.7% of the patients were women. The patients' mean age was 51 ± 19 years; 7.2% of them were between zero and 19.9 years of age; 21.3% between 20 and 39.9 years; 37.6% between 40 and 59.9 years; 28.2% between 60 and 79.9 years; and 5.0% greater than 80 years. In 0.7% of the examinations, the patient's age was not included. The youngest group was excluded from further evaluation here.

Table 1 shows the prevalences of self-reported comorbidities. **Tables 2A** and **2B** show the prevalences of electrocardiographic abnormalities according to sex and age groups. **Table 3** shows the ranking of the prevalences of electrocardiographic abnormalities according to sex and age groups.

Hypertension was the most frequent comorbidity, except in the group from 20 to 39.9 years of age, followed by a family history of coronary artery disease and smoking. In the group from 20 to 39.9 years of age, a family history of coronary artery disease was the most frequent risk factor for cardiovascular disease. From the age of 60 years, diabetes mellitus began to show significant prevalence: 11.4% and 6.5% respectively among men and women between 60 and 79.9 years of age and 9.3% and 5.3% among those aged 80 years and over. In general, the prevalence of comorbidities was higher in women of all age groups. The most common electrocardiographic abnormalities of all were nonspecific ventricular repolarization abnormalities, with prevalences ranging from 9.2% in women aged 20 to 39.9 years to 38.0% in those aged 80 and over (P = 0.008).

In the age group from 20 to 39.9 years, 80.6% of the tests in males and 70.7% in females were normal. The main electrocardiographic abnormality in women was left anterior hemiblock (LAH)[12] (1.0%), followed by complete right bundle branch block (RBBB) (0.8%). In men, early repolarization pattern (ERP) (4.1%) and LAH (2.4%) were the most prevalent.

Between 40 and 59.9 years of age, 66.1% and 59.9% of the examinations among women and men respectively were normal. Among women, the most common abnormalities remained similar to those of the younger age group described above, despite increases in their prevalence (3.6% for LAH and 2.2% for RBBB). Among men, these findings became predominant (6.8% and 3.3%, respectively) and the prevalences of left atrium enlargement and ventricle hypertrophy increased (3.3% and 4.1%, respectively).

In the age group from 60 to 79.9 years, 46.7% of females and 40.8% of males presented normal results from the tests. Left ventricular hypertrophy became the second most prevalent abnormal result, following LAH (4.8% in women, 7.0% in men). Left bundle branch block (LBBB) (3.3% and 2.9%, respectively), first-degree atrioventricular block (AVB) (2.2% and 3.9%) and atrial fibrillation and flutter (2.8% and 4.5%) became more frequent.

In patients aged greater than or equal to 80 years, 70.6% of the women and 75.8% of the men showed abnormalities on the electrocardiogram. In both sexes, there was significantly increased prevalence of atrial fibrillation and flutter, especially among men

(10.3%). In women, left ventricular hypertrophy remained a major result (8.7%), as did RBBB (6.2%), LBBB (6.3%) and LAH (13.2%). LAH was present in over 20% of examinations on males and first-degree AVB in 8.0%.

DISCUSSION

In this study, on a large sample of primary care patients, electrocardiographic abnormalities were relatively common findings, even in the younger age groups. In the age group from 20 to 39.9 years, 19.4% of the women and 29.3% of the men had at least one abnormal result. The prevalence of abnormalities increased with age and was higher among males in all age groups. Atrial fibrillation and flutter, premature beats, intraventricular block, complete right bundle branch block and left ventricle hypertrophy were more frequent among men. Women had higher prevalences of nonspecific ventricular repolarization abnormalities and complete left bundle branch block.

Most examinations (87.1%) were conducted on patients aged between 20 and 79.9 years. Women presented a higher proportion of self-reported comorbidities, except for smoking. This reinforces the findings in the literature on this subject, which indicate that women care more about their health and therefore tend to be more aware of their medical conditions.[12,13]

With regard to comorbidities and cardiovascular risk factors, hypertension was the most common one (34.2% and 28.9% in women and men, respectively) from 20 years of age onwards, followed by family history of coronary artery disease (16.0% and 13.6% in women and men). The prevalence of hypertension in the population aged 60-79.9 years in the present analysis (48.2%) was similar to what was found among subjects from 60 to 70 years of age (48.6%) in a cross-sectional study that investigated hypertension in the population of a Brazilian state capital.[14] In another study, in which household surveys were conducted in 15 Brazilian state capitals and in the federal district, the prevalence of self-reported hypertension among individuals aged 25-39 years (7.4% to 15.7%) was similar to what was found in the present study in the age group of 20-40 years.[15] The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) also had similar figures.[16] This suggests that our sample may be representative of the Brazilian population.

Sex differences regarding hypertension are well known, from epidemiology to pathophysiology to target organ damage. Women have higher awareness, treatment and control rates and lower prevalence of left ventricular hypertrophy (LVH).[7] This was seen in the sample of the present study: while reports of disease were higher in females, , males had higher prevalence of LVH in all age groups.

Self-reported diabetes was more frequent among females, mostly in individuals over 60 years of age. In the literature, slightly higher prevalence of diabetes in males has been reported worldwide. Nonetheless, studies from the Caribbean and from southern Africa showed higher prevalence of diabetes in women than

Table 1. Reported comorbidities and risk factors, according to sex and age group (n = 264,324)

Age group												
Comorbidity/ risk factors	20-39.9 years			40-59.9 years			60-79.9 years			> 80 years		
	F (n= 35,463)	M (n = 20,922)	P	F (n = 61,911)	M (n = 37,555)	P	F (n = 42,501)	M (n=31,973)	P	F (n = 7,596)	M (n = 5,685)	P
Hypertension	4,682 (13.20%)	2,549 (12.18%)	< 0.001	22,578 (36.47%)	11,364 (30.26%)	< 0.001	22,007 (51.78%)	13,917 (43.53%)	< 0.001	4,126 (54.32%)	2,677 (47.09%)	< 0.001
Chagas disease	490 (1.38%)	283 (1.35%)	0.774	2,346 (3.79%)	1,313 (3.50%)	0.017	1,755 (4.13%)	989 (3.09%)	< 0.001	252 (3.32%)	117 (2.06%)	< 0.001
Diabetes mellitus type 2	616 (1.74%)	282 (1.35%)	< 0.001	3,685 (5.95%)	1,625 (4.33%)	< 0.001	4,856 (11.43%)	2,082 (6.51%)	< 0.001	709 (9.33%)	304 (5.35%)	< 0.001
Dyslipidemia	370 (1.04%)	194 (0.93%)	0.181	2,104 (3.40%)	972 (2.59%)	< 0.001	2,284 (5.37%)	991 (3.10%)	< 0.001	309 (4.07%)	115 (2.02%)	< 0.001
Smoking	1,755 (4.95%)	904 (4.32%)	< 0.001	4,601 (7.43%)	4,699 (12.51%)	< 0.001	1,703 (4.01%)	3,255 (10.18%)	< 0.001	217 (2.86%)	430 (7.56%)	< 0.001
COPD	190 (0.54%)	67 (0.32%)	< 0.001	388 (0.63%)	186 (0.50%)	0.008	362 (0.85%)	337 (1.05%)	0.005	88 (1.16%)	93 (1.64%)	0.023
Chronic renal disease	159 (0.45%)	72 (0.34%)	0.061	331 (0.53%)	165 (0.44%)	0.039	227 (0.53%)	165 (0.52%)	0.758	31 (0.41%)	28 (0.49%)	0.512
History of myocardial infarction	105 (0.30%)	50 (0.24%)	0.211	379 (0.61%)	338 (0.90%)	< 0.001	430 (1.01%)	440 (1.38%)	< 0.001	71 (0.93%)	64 (1.13%)	0.295
Family history of coronary artery disease	5,547 (15.64%)	2,875 (13.74%)	< 0.001	10,394 (16.79%)	5,379 (14.32%)	< 0.001	6,780 (15.95%)	4,344 (13.59%)	< 0.001	1,079 (14.20%)	744 (13.09%)	0.067

F = female examinations; M = male examinations; P = P-value; COPD = chronic obstructive pulmonary disease.

in men, which was a pattern similar to the one found in the present study. This was possibly due to higher rates of obesity among females from such developing regions, since obesity is one of the greatest risk factors for diabetes.[17]

There were fewer smokers aged between 20 and 39.9 years than in the age groups of 40-59.9 and 60-79.9 years. This corroborates the results from several studies that have demonstrated reductions in smoking rates over recent decades, mainly influenced by

Table 2A. Electrocardiograms abnormalities according to sex and age group: rhythm abnormalities, atrioventricular block and intraventricular conduction defects (n = 264,324)

Age group												
Abnormalities	20-39.9 years			40-59.9 years			60-79.9 years			> 80 years		
	F (n = 35,463)	M (n = 20,922)	P	F (n = 61,911)	M (n = 37,555)	P	F (n = 42,501)	M (n = 31,973)	P	F (n = 7,596)	M (n = 5,685)	P
Rhythm disorders												
Sinus rhythm	33,855 (95.46%)	19,736 (94.33%)	< 0.001	59,228 (95.66%)	35,325 (94.06%)	< 0.001	39,623 (93.2%)	28,978 (90.6%)	< 0.001	6,662 (87.7%)	4,757 (83.7%)	< 0.001
Ectopic atrial rhythm	84 (0.23%)	43 (0.20%)	0.448	98 (0.15)	76 (0.20)	0.107	73 (0.2%)	85 (0.3%)	0.006	23 (0.3%)	22 (0.4%)	0.450
Multifocal atrial rhythm	1 (0.002%)	1 (0.004%)	0.706	3 (0.0%)	4 (0.0%)	0.290	8 (0.0%)	9 (0.0%)	0.466	4 (0.1%)	3(0.1%)	1.000
Pacemaker	20 (0.05%)	24 (0.11%)	0.017	130 (0.20%)	106 (0.28%)	0.023	245 (0.6%)	185 (0.6%)	1.000	75 (1.0%)	78 (1.4%)	0.048
Junctional rhythm	18 (0.05%)	15 (0.07%)	0.321	40 (0.06%)	23 (0.06%)	0.838	46 (0.1%)	56 (0.2%)	0.016	18 (0.2%)	16 (0.3%)	0.611
Atrial fibrillation and flutter	49 (0.13%)	49 (0.23%)	0.008	336 (0.54%)	448 (1.19%)	< 0.001	1,188 (2.8%)	1,429 (4.5%)	< 0.001	527(6.9%)	586 (10.3%)	< 0.001
Supraventricular extrasystole and ventricular extrasystole	5 (0.014%)	2 (0.009%)	0.640	25 (0.04%)	20 (0.05%)	0.355	64 (0.2%)	71 (0.2%)	0.029	45 (0.6%)	49 (0.9%)	0.075
Supraventricular extrasystole	213 (0.60%)	145 (0.69%)	0.182	458 (0.73)	356 (0.94%)	< 0.001	1,109 (2.6%)	1,228 (3.8%)	< 0.001	505 (6.6%)	464 (8.2%)	0.001
Ventricular extrasystole	253 (0.71%)	148 (0.70%)	0.934	897 (1.44%)	668 (1.77%)	< 0.001	1,489 (3.5%)	1,589 (5.0%)	< 0.001	480 (6.4%)	521 (9.2%)	< 0.001
Atrioventricular (AV) blocks												
AV block 1	185 (0.52%)	183 (0.87%)	< 0.001	533 (0.86%)	627 (1.66%)	< 0.001	939 (2.2%)	1,257 (3.9%)	< 0.001	396 (5.2%)	457 (8.0%)	< 0.001
AV 2:1 advanced	6 (0.0169%)	8 (0.038%)	0.121	15 (0.02%)	35 (0.09%)	< 0.001	36 (0.1%)	45 (0.1%)	0.024	20 (0.3%)	20 (0.4%)	0.425
Complete AV block	5 (0.014%)	7 (0.03%)	0.128	16 (0.02%)	16 (0.04%)	0.153	33 (0.1%)	28 (0.1%)	0.700	17 (0.2%)	22 (0.4%)	0.104
AV block 2	6 (0.0169%)	7 (0.03%)	0.211	12 (0.019%)	29 (0.07%)	< 0.001	28 (0.1%)	36 (0.1%)	0.042	16 (0.2%)	15 (0.3%)	0.590
AV block 2:1	0	0		3 (0.004%)	8 90.02%)	0.017	10 (0.0%)	9 (0.0%)	0.818	4 (0.1%)	6 (0.1%)	.343
Intraventricular blocks												
Left anterior hemiblock	370 (1.04%)	502 (2.39%)	< 0.001	2,198 (3.55%)	2,542 (6.76%)	< 0.001	3,566 (8.4%)	4,545 (14.2%)	< 0.001	1,004 (13.2%)	1,144 (20.1%)	< 0.001
Left posterior hemiblock	139 (0.39%)	187 (0.89%)	< 0.001	114 (0.18%)	154 (0.41%)	< 0.001	103 (0.2%)	118 (0.4%)	0.002	22 (0.3%)	16 (0.3%)	0.997
Complete right bundle branch block	296 (0.83%)	331 (1.58%)	< 0.001	1,360 (2.19%)	1,258 (3.34%)	< 0.001	1,804 (4.2%)	1,982 (6.2%)	< 0.001	474 (6.2%)	558 (9.8%)	< 0.001
Complete left bundle branch block	46 (0.129%)	38 (0.18%9)	0.123	580 (0.93%)	3,389 (0.90%)	0.556	1,408 (3.3%)	935 (2.9%)	0.003	480 (6.32%)	317 (5.58%)	0.077

F = female examinations; M = male examinations; P = P-value.

tobacco control initiatives such as tax increases on these products and creation of restrictions on public smoking, among other equally effective measures.

Octogenarians reported lower frequency of Chagas disease, diabetes mellitus, smoking and dyslipidemia than did younger subjects, thus indicating that people who reach older age groups usually have fewer comorbidities and cardiovascular risk factors, which may be related to survival bias.

The prevalence of chronic kidney disease (CKD) is very likely to be underestimated: about 0.5% among women and men over 60 years.

Table 2B. Electrocardiograms abnormalities according to sex and age group: enlargement and hypertrophy, ischemia and other abnormalities (n = 264,324)

Age group												
Abnormalities	20-39.9 years			40-59.9 years			60-79.9 years			> 80 years		
	F (n = 35,463)	M (n = 20,922)	P	F (n = 61,911)	M (n = 37,555)	P	F (n = 42,501)	M (n = 31,973)	P	F (n = 7,596)	M (n = 5,685)	P
Enlargement and hypertrophy												
Right atrial enlargement	38 (0.10%)	28 (0.13%)	0.371	81 (0.13%)	82 (0.21%)	0.001	103 (0.2%)	86 (0.3%)	0.509	16 (0.2%)	16 (0.3%)	0.477
Right ventricular enlargement	11 (0.03%)	30 (0.14%)	< 0.001	16 (0.02%)	36 (0.09%)	< 0.001	32 (0.1%)	45 (0.1%)	0.007	11 (0.1%)	10 (0.2%)	0.665
Left atrial hypertrophy	218 (0.61%)	238 (1.13%)	< 0.001	1,157 (1.86%)	1,245 (3.31%)	< 0.001	1,470 (3.5%)	1,785 (5.6%)	< 0.001	357 (4.7%)	308 (5.4%)	0.064
Left ventricular hypertrophy	152 (0.42%)	412 (1.96%)	< 0.001	1,055 (1.70%)	1,526 (4.06%)	< 0.001	2,036 (4.8%)	2,250 (7.0%)	< 0.001	658 (8.7%)	521 (9.2%)	0.324
Ischemia												
Subendocardial	16 (0.04%)	13 (0.06%)	0.278	135 (0.21%)	6 (0.25%)	0.233	233 (0.5%)	141 (0.4%)	0.042	79 (1.0%)	40 (0.7%)	0.051
Subepicardial	37 (0.10%)	51 (0.24%)	< 0.001	273 (0.44%)	276 (0.73%)	< 0.001	390 (0.9%)	333 (1.0%)	0.089	80 (1.1%)	51 (0.9%)	0.376
Q wave	10 (0.02%)	14 (0.06%)	0.031	136 (0.21%)	194 (0.51%)	< 0.001	189 (0.4%)	298 (0.9%)	< 0.001	51 (0.7%)	56 (1.0%)	0.049
Poor R wave progression	195 (0.549%)	286 (1.366%)	< 0.001	829 (1.33%)	922 (2.45%)	< 0.001	1,279 (3.0%)	1,642 (5.1%)	< 0.001	354 (4.7%)	381 (6.7%)	< 0.001
Other abnormalities												
ST segment elevation	79 (0.22%)	490 (2.34%)	< 0.001	136 (0.21%)	537 (1.42%)	< 0.001	120 (0.3%)	262 (0.8%)	< 0.001	36 (0.5%)	42 (0.7%)	0.051
ST segment depression	44 (0.12%)	27 (0.12%)	0.872	304 (0.49%)	165 (0.43%)	0.249	382 (0.9%)	278 (0.9%)	0.692	114 (1.5%)	53 (0.9%)	0.004
Peaked T waves	3 (0.008%)	9 (0.043%)	0.007	9 (0.01%)	24 (0.06%)	< 0.001	5 (0.0%)	26 (0.1%)	< 0.001	7 (0.1%)	7 (0.1%)	0.600
Long QT	7 (0.019%)	3 (0.01%)	0.642	21 (0.03%)	12 (0.03%)	0.869	26 (0.1%)	15 (0.0%)	0.433	5 (0.1%)	6 (0.1%)	0.546
WPWS	86 (0.24%)	66 (0.31%)	0.107	95 (0.15%)	79 (0.21)	0.037	48 (0.1%)	51 (0.2%)	0.103	9 (0.1%)	4 (0.1%)	0.418
Brugada pattern	5 (0.014%)	8 (0.038%)	0.068	4 (0.006%)	13 (0.034%)	0.001	4 (0.0%)	7 (0.0%)	0.224	0	0	
Low QRS	39 (0.109%)	13 (0.062%)	0.071	152 (0.24%)	83 (0.22%)	0.440	132 (0.3%)	139 (0.4%)	0.006	40 (0.5%)	29 (0.5%)	0.998
Early repolarization	112 (0.31%)	851 (4.06%)	< 0.001	106 (0.17%)	710 (1.89%)	< 0.001	78 (0.2%)	287 (0.9%)	< 0.001	6 (0.1%)	27 (0.5%)	< 0.001
Nonspecific ventricular repolarization abnormalities	3,278 (9.24%)	2,152 (10.28%)	< 0.001	12,578 (20.3%)	6,919 (18.42%)	< 0.001	12,994 (30.6%)	8,784 (27.5%)	< 0.001	2,890 (38.0%)	2,035 (35.8%)	0.008
Normal	28,599 (80.64%)	14,787 (70.67%)	< 0.001	40,945 (66.13%)	22,481 (59.86%)	< 0.001	19,843 (46.7%)	13,031 (40.8%)	< 0.001	2,232 (29.4%)	1,378 (24.2%)	< 0.001

F = female examinations; M = male examinations; P = P-value; WPWS = Wolff–Parkinson–White syndrome.

A study in Juiz de Fora, a city in the same Brazilian state, showed that the prevalence in the same age group was 25.2%. It is possible that many patients were not aware of their condition, which thus emphasizes the need for screening, especially among individuals with high blood pressure and diabetes, which are the leading risk factors for CKD.[18]

Differences between the sexes regarding the cardiovascular system result from differences in gene expression from the sex chromosomes. This can also be further modified through the influence of sex-related hormones and other environmental factors, thereby resulting in sex-specific gene expression.[8] Thus, electrocardiographic

Table 3. Ranking of electrocardiograms abnormalities according to sex and age group (n = 264,324)

Age group								
Abnormalities	20-39.9 years		40-59.9 years		60-79.9 years		≥ 80 years	
	F (n = 35,463)	M (n = 20,922)	F (n = 61,911)	M (n = 37,555)	F (n = 42,501)	M (n = 31,973)	F (n = 7,596)	M (n = 5,685)
Rhythm disorders								
Ectopic atrial rhythm	13	16	21	22	22	22	20	21
Multifocal atrial rhythm	33	33	33	34	32	33	33	33
Pacemaker	21	21	18	18	14	17	15	12
Junctional rhythm	22	22	24	27	25	24	23	25
Atrial fibrillation and flutter	15	15	11	12	9	8	4	3
Supraventricular extrasystole and ventricular extrasystole	29	32	25	28	23	23	17	16
Supraventricular extrasystole	6	12	10	13	10	10	5	7
Ventricular extrasystole	4	11	6	9	5	7	7	6
Atrioventricular (AV) blocks								
AV block 1	8	10	9	10	11	9	9	8
AV block 2:1 advanced	27	27	29	24	26	26	22	23
Complete AV block	30	30	27	29	27	29	24	22
AV block 2	28	29	30	25	29	28	26	27
AV block 2:1	34	34	34	32	31	32	32	31
Intraventricular blocks								
Left anterior hemiblock	2	3	2	3	2	2	2	2
Left posterior hemiblock	10	9	19	17	19	20	21	24
Complete right bundle branch block	3	6	3	5	4	4	8	4
Complete left bundle branch block	16	17	8	2	7	11	6	10
Enlargement and hypertrophy								
Right atrial enlargement	19	19	23	20	20	21	25	26
Right ventricular enlargement	24	18	28	23	28	27	27	28
Left atrial hypertrophy	5	8	4	6	6	5	10	11
Left ventricular hypertrophy	9	5	5	4	3	3	3	5
Ischemia								
Subendocardial	23	24	17	33	15	18	14	18
Subepicardial	20	14	13	14	12	12	13	15
Q wave	25	23	15	15	16	13	16	13
Poor R wave progression	7	7	7	7	8	6	11	9
Other abnormalities								
ST segment elevation	14	4	16	11	18	16	19	17
St segment depression	17	20	12	16	13	15	12	14
Peaked T waves	32	26	31	26	33	30	29	29
Long QT	26	31	26	31	30	31	31	30
WPWS	12	13	22	21	24	25	28	32
Brugada	31	28	32	30	34	34	34	34
Low QRS	18	25	14	19	17	19	18	19
Early repolarization	11	2	20	8	21	14	30	20
Nonspecific changes of ventricular repolarization	1	1	1	1	1	1	1	1

F = female examinations; M = male examinations; WPWS = Wolff-Parkinson-White syndrome.

abnormalities may show primary differences between men and women. In the present study, 33.9% of the women and 40.1% of the men aged 40-59.9 years presented abnormal examinations. This was similar to the findings of another Brazilian study that also evaluated such abnormalities stratified by age, although this other study did not examine the prevalence in relation to sex and also included patients from secondary care.[19]

LAH was one of the most common disorders in all age groups, with increasing prevalence according to age. It may be caused by hypertension, cardiomyopathies, Chagas disease in endemic countries and Lev and Lenegre disease, and may form part of a benign senile degenerative process.[20] However, this abnormality has little or no correlation with poor prognosis and is poorly associated with higher numbers of comorbidities.[20] The prevalence rates for LAH in the combined population aged 40-79.9 years were 5.5% for women and 10.2% for men. This was compatible with several studies that have indicated that the prevalences of left axis deviation (which could be an indicator of LAH) and of LAH among men are around twice as high as among women.[3] One example of such findings comes from an Indian study in which different rates of abnormal ECG results between the sexes were observed among people aged 45-74 years: 5.7% for women and 9.6% for men. There was also strong agreement regarding the prevalence of left ventricular hypertrophy between this Indian study and the present study: 2.9% and 5.1% in the present study, versus 2.8% and 4.6% in the Indian study, in women and men respectively.[6]

The prevalence of atrial fibrillation was strongly associated with greater age, and it was higher in men than in women, in all age groups. Our findings regarding the prevalence of atrial fibrillation according to age and sex were similar to data from high-income countries.[11] This confirms and extends the findings of a previous paper from our group,[21] from a subsample of the data used in the present study that was analyzed without the Minnesota Code. Since atrial fibrillation is a major risk factor for stroke, but there is no national health policy to promote primary and secondary stroke prevention among patients with atrial fibrillation (the new oral anticoagulants are not provided through the public health system and there are not enough anticoagulation clinics to control patients on warfarin),[22] the data provided by the present study is very important for stakeholders.

Another very frequent finding in all age groups was RBBB, which gives rise to a threefold increased risk of cardiovascular events and has been correlated with larger numbers of comorbidities.[23] RBBB also presented increasing prevalence with age, as had already been observed in the evaluation on RBBB within the Copenhagen City Heart Study.[24] Complete RBBB had higher prevalence in the present study than in the Danish study (4.0% and 2.5% in men and women respectively, versus 1.5% and 0.5%).[24] One hypothesis that would explain this discrepancy is the higher number of patients with Chagas disease in Brazil.

It has been well established that men present higher frequencies of intraventricular block and RBBB than do women.[25] This was also found in the present study in relation to LAH, left posterior hemiblock and RBBB, but not in relation to LBBB. A statistically significant difference in the frequency of LBBB between men and women was only present in the age group from 60 to 79.9 years, which is understandable, given the usually late onset of LBBB.[26] In this group, the prevalence was 2.9% in men and 3.3% in women. Other studies have also found similar prevalences of LBBB in both sexes[3,26] but none of them further explored the slightly higher prevalence of LBBB among women.

Nonspecific ventricular repolarization abnormalities were the most prevalent abnormalities in all age groups. This is consistent with the previously mentioned American study that evaluated electrocardiographic disorders in 20,962 people according to sex and age.[5] These abnormalities have been correlated with significantly higher risk of fatal coronary heart disease,[27] for which primary arrhythmia is the main mechanism.[28] This ECG disorder was more prevalent among women, and this might be explained by the significant influence of sex hormones on the QT interval in women: whereas this component is only shortened through the influence of testosterone in men, significant estrogen activity in women prolongs this interval while their progesterone acts similarly to testosterone.[29] These nonspecific repolarization abnormalities were also found to be predictors of CHD events and CHD death among postmenopausal women.[30]

Chagas disease is still highly prevalent in Brazil. Out of the 5.7 million people chronically infected in Latin America, 20% are in this country.[31] The most common electrocardiographic findings in Chagas disease are RBBB (22.7%) and LAH (22.5%). In addition to these, second and third-degree atrioventricular blocks and atrial fibrillation are also strongly associated with Chagas disease.[32] In the present study, 2.9% of the patients reported having Chagas disease and, as previously described, this may explain the higher prevalence of RBBB in relation to other studies.[27]

Left ventricular hypertrophy (LVH) is an independent predictor of morbidity and cardiovascular mortality and tends to increase with age.[33] The risk is particularly increased when associated with ventricular repolarization abnormalities.[34] The main etiologies of left ventricle hypertrophy are hypertension, hypertrophic cardiomyopathy and dilated cardiomyopathy, coronary artery disease, valvular disease, obesity, diabetes mellitus, drug abuse and chronic kidney disease.[35] In the present study, although the prevalence of hypertension was similar to that of other studies, as already mentioned, left ventricular hypertrophy remained below 10%, even in older individuals: 1.7% in women and 4.0% in men aged 40 to 59; 4.8% and 7.0% respectively between the ages of 60 and 79 years; and 8.7% and 9.2% among individuals aged 80 years and over. One hypothesis to explain this discrepancy is the low sensitivity of electrocardiograms for detecting this abnormality, in comparison with echocardiograms.[33]

Interestingly, ECG abnormalities suggestive of acute ischemia, i.e. signs of subendocardial and subepicardial injury, were 0.3% and 0.6% overall, even though the present study was on tests performed within primary care. These cases are supposed to be attended in emergency centers. However, many of the municipalities studied here do not have any emergency units or hospitals, and therefore patients seek care for emergency conditions at primary care centers. In addition, many patients become so used to attending primary care centers that they seek help there even in emergency situations.

This study has certain limitations. The comorbidities and medications were self-reported, so they may have been underreported. The electrocardiographic reports followed predetermined patterns, using criteria established by the Brazilian Society of Cardiology.[10] These criteria have not yet been validated in as many population-based studies as the Minnesota code.[36] However, the criteria used reflect current practices in Brazil, thus ensuring the ability to generalize the results to other primary care settings in this country.

CONCLUSION

This study on a large sample of primary care patients showed that electrocardiographic abnormalities were relatively common findings, even in the younger age groups. The prevalence of abnormalities increased with age and was higher in men in all age groups, even though women had higher frequency of self-reported comorbidities. Atrial fibrillation and flutter, premature beats, intraventricular blocks, complete right bundle branch block and left ventricle hypertrophy were more frequent in men. Women had higher prevalence of nonspecific ventricular repolarization abnormalities and complete left bundle branch block.

The correlations of age and sex with electrocardiographic abnormalities that were made through the present study may help towards increasing the predictive value of ECGs and contribute towards diagnosing and subsequently managing many common cardiovascular diseases within primary care. Furthermore, the findings from this study reinforce the importance of consolidating programs for prevention and screening of diseases that enhance cardiovascular risk such as hypertension, diabetes, hyperlipidemia and smoking.

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
2. Kankeu HT, Saksena P, Xu K, Evans DB. The financial burden from non-communicable diseases in low- and middle-income countries: a literature review. Health Res Policy Syst. 2013;11:31.
3. De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. Heart. 2000;84(6):625-33.
4. Denes P, Larson JC, Lloyd-Jones DM, Prineas RJ, Greenland P. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. JAMA. 2007;297(9):978-85.
5. Prineas RJ, Le A, Soliman EZ, et al. United States national prevalence of electrocardiographic abnormalities in black and white middle-age (45- to 64-Year) and older (≥ 65-Year) adults (from the Reasons for Geographic and Racial Differences in Stroke Study). Am J Cardiol. 2012;109(8):1223-8.
6. Sachin Khane R, Surdi AD. Gender differences in the prevalence of electrocardiogram abnormalities in the elderly: a population survey in India. Iran J Med Sci. 2012;37(2):92-9.
7. Doumas M, Papademetriou V, Faselis C, Kokkinos P. Gender differences in hypertension: myths and reality. Curr Hypertens Rep. 2013;15(4):321-30.
8. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular Disease in Women: Clinical Perspectives. Circ Res. 2016;118(8):1273-93.
9. Alkmim MB, Figueira RM, Marcolino MS, et al. Improving patient access to specialized health care: the Telehealth Network of Minas Gerais, Brazil. Bull World Health Organ. 2012;90(5):373-8.
10. Sociedade Brasileira de Cardiologia. Diretrizes da Sociedade Brasileira de Cardiologia sobre Análise e Emissão de Laudos Eletrocardiográficos (2009 [Guidelines of Sociedade Brasileira de Cardiologia about analysis and issuance of expert opinion in electrocardiographic (2009)]. Arq Bras Cardiol. 2009;93(3 Supl 2):2-19.
11. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.
12. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract. 2000;49(2):147-52.
13. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005;49(6):616-23.
14. Souza ARA, Costa A, Nakamura D, et al. Um estudo sobre hipertensão arterial sistêmica na cidade de Campo Grande, MS [A study on systemic arterial hypertension in Campo Grande, MS, Brazil]. Arq Bras Cardiol. 2007;88(4):441-6.
15. Passos VMA, Assis TD, Barreto SM. Hipertensão arterial no Brasil: estimativa de prevalência a partir de estudos de base populacional [Hypertension in Brazil: estimates from population-based prevalence studies]. Epidemiol Serv Saude. 2006;15(1):35-45.
16. Chor D, Pinho Ribeiro AL, Sá Carvalho M, et al. Prevalence, Awareness, Treatment and Influence of Socioeconomic Variables on Control of High Blood Pressure: Results of the ELSA-Brasil Study. PloS One. 2015;10(6):e0127382.
17. Sobers-Grannum N, Murphy MM, Nielsen A, et al. Female gender is a social determinant of diabetes in the Caribbean: a systematic review and meta-analysis. PloS One. 2015;10(5):e0126799.
18. Bastos RMR, Bastos MG, Ribeiro LC, Bastos RV, Teixeira MTB. Prevalência da doença renal crônica nos estágios 3, 4 e 5 em adultos [Prevalence of chronic kidney disease, stages 3, 4 and 5 in adults]. Rev Assoc Med Bras (1992). 2009;55(1):40-4.

19. Giuliano ICB, Barcellos Junior CL, von Wangenheim A, Coutinho MSSA. Emissão de laudos eletrocardiográficos a distância: experiência da rede catarinense de telemedicina [Issuing electrocardiographic reports remotely: experience of the telemedicine network of Santa Catarina]. Arq Bras Cardiol. 2012;99(5):1023-30.
20. Elizari MV, Acunzo RS, Ferreiro M. Hemiblocks revisited. Circulation. 2007;115(9):1154-63.
21. Marcolino MS, Palhares DM, Benjamin EJ, Ribeiro AL. Atrial fibrillation: prevalence in a large database of primary care patients in Brazil. Europace. 2015;17(12):1787-90.
22. Marcolino MS, Polanczyk CA, Bovendorp AC, et al. Economic evaluation of the new oral anticoagulants for the prevention of thromboembolic events: a cost-minimization analysis. Sao Paulo Med J. 2016;134(4):322-9.
23. Schneider JF, Thomas HE, Kreger BE, et al. Newly acquired right bundle-branch block: The Framingham Study. Ann Intern Med. 1980;92(1):37-44.
24. Bussink BE, Holst AG, Jespersen L, et al. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. Eur Heart J. 2013;34(2):138-46.
25. Kreger BE, Anderson KM, Kannel WB. Prevalence of intraventricular block in the general population: the Framingham Study. Am Heart J. 1989;117(4):903-10.
26. Imanishi R, Seto S, Ichimaru S, et al. Prognostic significance of incident complete left bundle branch block observed over a 40-year period. Am J Cardiol. 2006;98(5):644-8.
27. Ribeiro AL, Sabino EC, Marcolino MS, et al. Electrocardiographic abnormalities in Trypanosoma cruzi seropositive and seronegative former blood donors. PLoS Negl Trop Dis. 2013;7(2):e2078.
28. Kumar A, Prineas RJ, Arnold AM, et al. Prevalence, prognosis, and implications of isolated minor nonspecific ST-segment and T-wave abnormalities in older adults: Cardiovascular Health Study. Circulation. 2008;118(25):2790-6.
29. Ganjehei L, Massumi A, Nazeri A, Razavi M. Cardiac arrhythmias in women. Tex Heart Inst J. 2011;38(2):157-9.
30. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113(4):473-80.
31. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec. 2015;90(6):33-43.
32. Marcolino MS, Palhares DM, Ferreira LR, Ribeiro AL. Electrocardiogram and Chagas disease: a large population database of primary care patients. Global Heart. 2015;10(3):167-72.
33. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561-6.
34. Kannel WB, Dannenberg AL, Levy D. Population implications of electrocardiographic left ventricular hypertrophy. Am J Cardiol. 1987;60(17):85I-93I.
35. Gasperin CA, Germiniani H, Facin CR, Souza AM, Cunha CLP. Análise dos critérios eletrocardiográficos para determinação de sobrecarga ventricular esquerda [An analysis of electrocardiographic criteria for determining left ventricular hypertrophy]. Arq Bras Cardiol. 2002;78(1):72-82.
36. Marty AT. Minnesota Code Manual of Electrocardiographic Findings. Critical Care Medicine. 1983;11(7):583. Available from: http://journals.lww.com/ccmjournal/Citation/1983/07000/Minnesota_Code_Manual_of_Electrocardiographic.29.aspx. Accessed in 2017 (Sep 18).

This study was presented at the 42nd International Congress of Electrocardiology, held in Comandatuba, Bahia, Brazil, on June 26, 2015

Sources of funding: The Telehealth Network of Minas Gerais is sponsored by the State Government of Minas Gerais, by its Health Department (Secretaria de Estado da Saúde de Minas Gerais) and its research agency FAPEMIG (Fundação de Amparo à Pesquisa de Minas Gerais); and by the Brazilian Government, including the Ministry of Health and the Ministry of Science and Technology and their research and innovation agencies, CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and FINEP (Financiadora de Estudos e Projetos). This study was sponsored by FAPEMIG, the research agency of the state of Minas Gerais, Brazil (grant number CDS-RED-00004-14). ALR was supported in part by CNPq (research productivity bursary 309073/2011-1), ,FAPEMIG (PPM-00428-17) and Instituto Nacional de Ciência e Tecnologia para Avaliação de Tecnologias em Saúde (project CNPq/465518/2014-1). DFAJ was supported by the Pro-Rectorate for Research (Pró-Reitoria de Pesquisa, PRPq) of the Federal University of Minas Gerais (PIBIC/CNPq). JPAS received a grant from CNPq (grant number 180404/2014-8)

Conflict of interest: None declared

Date of first submission: July 16, 2017
Last received: July 16, 2017
Accepted: August 29, 2017

Address for correspondence:
Milena Soriano Marcolino
Av. Professor Alfredo Balena, 190 — Sala 246
Belo Horizonte (MG) — Brasil
CEP 30130-100
E- mail: milenamarc@gmail.com

DOI: 10.1590/1516-3180.2017.0109100917

C-reactive protein/albumin ratio is associated with lung function among children/adolescents with cystic fibrosis: a three-year longitudinal study

Julia Carvalho Ventura[I], Daniela Barbieri Hauschild[I], Emília Addison Machado Moreira[II], Letícia Cristina Radin Pereira[III], Anauã Franco Rosa[IV], Eliana Barbosa[V], Norberto Ludwig-Neto[VI], Julia Salvan da Rosa[VII], Tânia Silvia Fröde[VIII], Yara Maria Franco Moreno[II]

Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil

[I]MSc. Doctoral Student, Postgraduate Program on Nutrition, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
orcid.org/0000-0002-0492-0352

[II]PhD. Professor, Department of Nutrition and Postgraduate Program on Nutrition, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.

[III]MSc. Doctoral Student, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada.

[IV]BSc. Dietitian, Florianópolis (SC), Brazil.

[V]MSc. Dietitian, Joana de Gusmão Children's Hospital. Florianópolis (SC), Brazil.

[VI]MD. Physician, Joana de Gusmão Children's Hospital. Florianópolis (SC), Brazil.

[VII]MSc. Doctoral Student, Department of Clinical Analysis, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.

[VIII]PhD. Professor, Department of Clinical Analysis, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
orcid.org/0000-0002-4983-2911

KEY WORDS:
Cystic fibrosis.
Nutritional status.
Lung diseases.
C-reactive protein.
Serum albumin.

ABSTRACT

BACKGROUND: Chronic lung infections, inflammation and depletion of nutritional status are considered to be prognostic indicators of morbidity in patients with cystic fibrosis. The aim of this study was to investigate the association between inflammatory markers and lung function, nutritional status and morbidity among children/adolescents with cystic fibrosis.

DESIGN AND SETTINGS: Prospective three-year longitudinal study conducted in an outpatient clinic in southern Brazil.

METHODS: Children/adolescents aged 1-15 years with cystic fibrosis were enrolled. Nutritional status was determined from weight-to-length and body mass index-to-age z-scores and was classified as acceptable, at risk or nutritional failure. Tumor necrosis factor-α, interleukin-1β, myeloperoxidase, C-reactive protein and C-reactive protein/albumin ratio were analyzed. Lung function was evaluated based on the forced expiratory volume in the first second and morbidity according to the number of hospitalizations for pulmonary exacerbation and infections by *Pseudomonas aeruginosa*. Lung function, nutritional status and morbidity were the outcomes. Odds ratios and 95% confidence intervals were to evaluate the effect of baseline inflammatory markers on the clinical outcomes after three years of follow-up and p-values < 0.05 were considered significant.

RESULTS: We evaluated 38 children/adolescents with cystic fibrosis: 55% female; median age (with interquartile range), 3.75 years (2.71-7.00). Children/adolescents with high C-reactive protein/albumin ratio at baseline had odds of 18 (P = 0.018) of presenting forced expiratory volume in the first second ≤ 70% after three years. The other inflammatory markers were not associated with the outcomes.

CONCLUSION: C-reactive protein/albumin ratio was associated with forced expiratory volume in the first second ≤ 70% after three years.

INTRODUCTION

Cystic fibrosis is an autosomal recessive genetic disease resulting from abnormal functioning of the transmembrane protein that regulates ionic transport: the cystic fibrosis transmembrane conductance regulator. It leads to a set of manifestations and complications, such as the presence of thick, viscous secretions and obstruction of exocrine gland ducts, thus compromising the respiratory and digestive systems.[1]

Lung disease is the fundamental cause of morbidity and mortality in cystic fibrosis. Individuals affected by cystic fibrosis rarely demonstrate respiratory symptoms at birth. However, within a short time, the combination of obstruction, inflammation and infection begins to exert a negative effect on lung growth, structure and function.[1,2]

Bacterial infection, due to *Pseudomonas aeruginosa*, *Staphylococcus aureus* or the *Burkholderia cepacia* complex, for example, can adapt to the lung environment. It may affect the host's defenses through bacterial adherence to the thick mucus or through secretion of extracellular polysaccharides, thereby favoring chronic bacterial infection and providing continuous stimulation of an inflammatory response.[3]

Persistent neutrophil infiltration leads to hyperactivation of nuclear transcription factor-kappa B, which promotes overexpression of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β.[4] The continuous inflammatory response and persistent inflammation in individuals with cystic fibrosis lead to an imbalance in cytokine levels, thus stimulating hepatic

production of acute-phase proteins, such as C-reactive protein.[5] High levels of C-reactive protein are associated with lower forced expiratory volume in the first second in individuals with cystic fibrosis.[6] In addition to C-reactive protein levels, the C-reactive protein/albumin ratio can be evaluated and used as an inflammatory-nutritional factor.[7]

The systemic inflammatory response is associated with a continuous catabolic response, which exerts an effect on fat-free mass and leads to reduced skeletal muscle mass and wastage of inspiratory muscles.[8] Thus, nutritional status, body composition and inflammatory conditions are considered to be prognostic indicators of morbidity and mortality among individuals with cystic fibrosis.[9]

OBJECTIVE

The aim of the present study was to analyze the association between inflammatory markers (tumor necrosis factor-α, interleukin-1β, myeloperoxidase, C-reactive protein and C-reactive protein/albumin ratio) and lung function, nutritional status and morbidity among children/adolescents with cystic fibrosis.

METHODS

Study design, participants and ethics

A three-year prospective longitudinal study was conducted between April 2009 and December 2012 involving children/adolescents aged 1-15 years with a diagnosis of cystic fibrosis through the sweat test or newborn screening. The participants were recruited at an interdisciplinary cystic fibrosis outpatient clinic in southern Brazil.

A non-probabilistic convenience sample based on temporal saturation that was recruited between April 2009 and July 2010 was used. The inclusion criteria were that the subjects needed to be 1-15 years of age and have a diagnosis of cystic fibrosis that had been confirmed through an abnormal sweat test (chloride in sweat ≥ 60 mmol/l).[10] The exclusion criteria were the presence of pulmonary exacerbation, fever, trauma, inflammatory disease (asthma, intestinal inflammatory disease and rheumatic disease), psychiatric disorder, degenerative condition, cardiovascular disease, diabetes, glucose intolerance, kidney failure, primary or secondary immunodeficiency, and use of anti-inflammatory and/or immunosuppressive drug treatment. Children/adolescents with a negative sweat test or who discontinued their treatment at the hospital were also excluded.

Considering the lack of a cutoff point for the inflammatory markers, a group without cystic fibrosis was selected among patients at the child care clinic in order to determine the cutoff points for tumor necrosis factor-α, interleukin-1β, myeloperoxidase, C-reactive protein and C-reactive protein/albumin ratio. The inclusion criteria for the group without cystic fibrosis comprised absence of a diagnosis of cystic fibrosis and being within the range of good health and ideal nutrition, as determined by a weight-to-length z-score or body mass index-to-age z-score between -2 and +2.[11]

Data collection, at the baseline of the study, involved determination of anthropometric data, lung function and inflammatory markers. Clinical data (use of enzymes) and patient identification were also collected at the baseline of the study, from patient charts. Outcome data on lung function, nutritional status and morbidity (positive cultures, number of hospitalizations and respective causes) were collected from patient charts after a three-year follow-up.

The study was approved by the local institutional review board (human research ethics committee). Informed consent was obtained from the parents or guardians of all the patients enrolled in the study.

Nutritional status evaluation

Weight was determined using a digital pediatric scale (Filizola, São Paulo, Brazil) for children up to two years of age and a standard scale (Balmak model BK 50 F, São Paulo, Brazil) for individuals over two years of age. Length was measured using a children's stadiometer with a movable plate (Sanny, São Paulo, Brazil) for children up to two years of age and height was determined using a length board (Alturaexata, Minas Gerais, Brazil) for individuals over two years of age.[12]

Weight-to-length percentiles were calculated for children up to two years of age and body mass index-to-age percentiles for individuals over two years of age, using reference curves.[12] Nutritional status was classified based on the recommendations of the American Cystic Fibrosis Foundation,[13] as nutritional failure (< 10^{th} percentile), at risk (10^{th} to 25^{th} percentile) or acceptable (> 25^{th} percentile). Nutritional status was considered ideal when weight-to-length was ≥ 50^{th} percentile for children up to two years of age, and when body mass index-to-age was ≥ 50^{th} percentile for individuals over two years of age.[14]

Lung function evaluation

A spirometer (Renaissance Spirometry System, Puritan-Bennet Corporation, North Carolina, USA) was used for individuals aged six years and over, since children younger than six years have lower capacity to perform voluntary respiration maneuvers in an efficient manner.[15] Spirometry was supervised by a trained professional, following the recommendations of the American Thoracic Society (Puritan-Bennett Corporation, North Carolina, USA). Respiratory obstruction was evaluated based on the forced expiratory volume in the first second, taking the forced expiratory volume in the first second to be ≤ 70%.[16]

Bacterial evaluation

After a state of oral hygiene had been achieved, samples of oropharyngeal secretion were collected using a sterile swab

that was introduced into the oropharyngeal cavity following deep coughing effort. These samples were processed using the method described by Gilligan et al.[17] All sample collection was performed by a trained professional. The evaluation was performed under a microscope (Nikon E200, Tokyo, Japan), using the Gram method.[18]

Inflammatory markers

Peripheral venous blood (10 ml) was collected from the cubital vein after the patient had been fasting for 10 hours. Serum was obtained, separated into aliquots and stored at -80 °C until processing to determine the study parameters.

The inflammatory markers analyzed were tumor necrosis factor-α, interleukin-1β, myeloperoxidase and C-reactive protein levels. The serum levels of tumor necrosis factor-α and interleukin-1β were determined using an enzyme-linked immunosorbent assay.[19] The results were expressed as pg/ml. The C-reactive protein level was determined using the nephelometric method (Behring Nephelometer BN 2, Berlin, Germany) and the data were expressed as mg/dl. Myeloperoxidase activity was measured using the colorimetric method developed by Rao et al.[20] and was read with absorbance at 450 nm in an enzyme-linked immunosorbent assay reader (Organon-Tecknica, New Jersey, USA); the results were expressed as mU/ml. The albumin level was determined using bromocresol green with the aid of a specific kit (Labtest Diagnóstica, Labtest, Minas Gerais, Brazil), using a colorimetry assay, and the data were expressed as g/dl.[21] The C-reactive protein/albumin ratio was determined by dividing the C-reactive protein values by the albumin values, and the data were expressed as mg/dl:g/dl.[22]

Morbidity, clinical condition and pancreatic function

Morbidity was evaluated based on the frequency of hospitalizations due to pulmonary exacerbation[23] and infections by *Pseudomonas aeruginosa* over the three-year period. Presence of infection was established as a count greater than 10^4 colony-forming units.

The Shwachman-Kulczycki score was used to classify clinical condition, with points attributed to general activities, physical examination, nutritional status and radiological findings. A score of ≥ 86 points was considered to be excellent, 71 to 85 good, 56 to 70 average, 41 to 55 poor and ≤ 40 severe.[24] In accordance with the standard medical regimen, patients who used pancreatic enzymes were classified as having pancreatic insufficiency.[25]

Statistical analysis

The statistical analysis was performed using the STATA software, version 11.0 (Stata Corp., Texas, USA). Quantitative variables were expressed as means and standard deviations or as medians and interquartile ranges, depending on the symmetry. Nominal variables were expressed as percentages and 95% confidence intervals. The t test or Mann-Whitney test, when appropriate, was used to determine differences between means. Pearson's or Fisher's chi-square test, when appropriate, was used to determine the strength of associations between the categorical variables. Odds ratios and 95% confidence intervals were calculated to evaluate the effect of baseline inflammatory markers on the clinical outcomes after three years of follow-up. Inflammatory markers were classified as "adequate" or "high", using the 90th percentile in the group without cystic fibrosis as the cutoff point. P-values < 0.05 were considered significant.

RESULTS

At the baseline of the study, 49 children/adolescents with cystic fibrosis were recruited, and 38 of them met the eligibility criteria (**Figure 1**).

The median age of the children with cystic fibrosis (n = 38) was 3.75 years (interquartile range: 2.71 to 7.00 years) and 55% were female. The median age at which cystic fibrosis was diagnosed was 3.50 months (interquartile range: 2.00 to 11.00 months). Their mean forced expiratory volume in the first second was 76.67% ± 19.90% and the Shwachman-Kulczycki score was 86.76 ± 17.92 (**Table 1**).

In the group without cystic fibrosis (n = 31), the median age was 4.62 years (interquartile range: 3.04 to 8.91) and 61% were female. There were no significant differences in sex and age between the groups at the baseline (**Table 1**).

Regarding the classification of nutritional status based on the criteria of the American Cystic Fibrosis Foundation (2009), 22 children/adolescents (58%) were classified as having acceptable nutritional status (> 25th percentile) and 25 (66%) were considered to have ideal nutritional status (≥ 50th percentile) according to their weight-to-length or body mass index-to-age percentile (**Table 1**). In comparing the nutritional status between groups, 19 (61%) of the children/adolescents without cystic fibrosis were considered to have ideal nutritional status (≥ 50th percentile) while 13 (34%) of the children/adolescents with cystic fibrosis were considered to have ideal nutritional status (≥ 50th percentile), according to the weight-to-length or body mass index-to-age percentile (P = 0.025) (**Table 1**).

At the baseline of the study, higher median interleukin-1β and myeloperoxidase values were found in the cystic fibrosis group than in the group without cystic fibrosis (P < 0.001). The median C-reactive protein/albumin ratio was also higher in the cystic fibrosis group, but the difference was not significant (P = 0.077) (**Table 2**).

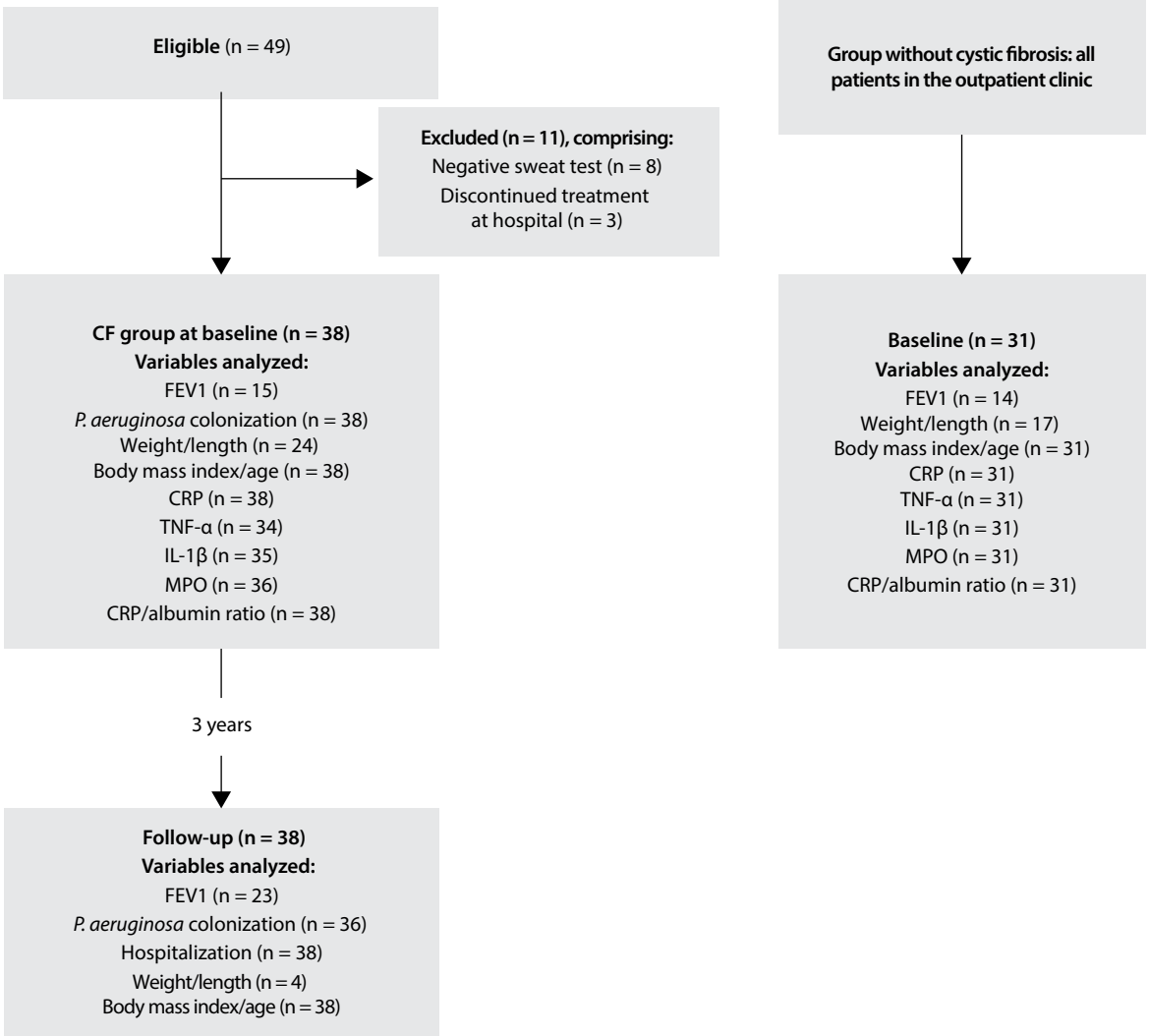
High C-reactive protein/albumin ratio at the beginning of the study was associated with forced expiratory volume in the first second ≤ 70% after three years of follow-up, in comparison with those with a normal C-reactive protein/albumin

ratio, with odds of 18.00 (95% confidence interval: 1.63; 198.51) (P = 0.018). The C-reactive protein/albumin ratio was not associated with hospitalization (odds ratio: 2.00; 95% confidence interval: 0.52; 7.70), or with a positive culture for *Pseudomonas aeruginosa* (odds ratio: 0.65; 95% confidence interval: 0.10; 4.14), or with body mass index-to-age < 50th percentile (odds ratio: 1.96; 95% confidence interval: 0.42; 9.10). Tumor necrosis factor-α, interleukin-1β, myeloperoxidase and C-reactive protein levels were not associated with lung function, hospitalization, positive culture for *Pseudomonas aeruginosa* or nutritional status. However, patients with high myeloperoxidase activity and adequate tumor necrosis factor-α levels at the baseline had positive cultures for *Pseudomonas aeruginosa* after three years (**Table 3**).

DISCUSSION

Associations between the C-reactive protein/albumin ratio and lung function, nutritional status, positive culture for *Pseudomonas aeruginosa* and hospitalization among patients with cystic fibrosis have been little investigated. In the present study, children/adolescents with higher C-reactive protein/albumin ratio at the baseline had higher odds of forced expiratory volume in the first second ≤ 70% after three years of follow-up.

Unlike monitoring using sputum, the advantage of systemic monitoring of inflammation via blood sampling is that it has the potential to reflect the inflammatory status throughout the lungs, as opposed to in just one region.[26] In the present study, we evaluated serum biomarkers in children/adolescents with cystic fibrosis



CRP = C-reactive protein; FEV1 = forced expiratory volume in first second; IL-1β = interleukin 1 beta; MPO = myeloperoxidase; n = absolute number; *P. aeruginosa* = *Pseudomonas aeruginosa*; TNF-α = tumor necrosis factor-alpha.

Figure 1. Flowchart of selection of children/adolescents with (CF group) and without cystic fibrosis in follow-up, 2009-2012.

and found that the interleukin-1β and myeloperoxidase levels were significantly higher in the cystic fibrosis group than in the group without cystic fibrosis. However, there was no difference in tumor necrosis factor-α levels. On the other hand, a previous study reported that the tumor necrosis factor-α level was significantly higher in the cystic fibrosis group than in a control group, which might have resulted from bacterial infections, such as with *Staphylococcus aureus*, or from other microorganisms.[27]

Situations of increased inflammation in cystic fibrosis patients are well known, and the clinical course of the lung disease in cystic fibrosis cases probably depends on the nature and degree of the inflammatory response.[27] In a study on 35 children with cystic fibrosis, aged 6 to 15 years, the levels of tumor necrosis factor-α, interleukin-1β and IL-6 in the sputum changed over a three-year period and a single determination of these markers had predictive value for a subsequent percentage decline in predicted forced expiratory volume in the first second.[28] However, in the present investigation, C-reactive protein, tumor necrosis factor-α, interleukin-1β levels and myeloperoxidase activity at the baseline were not associated with forced expiratory volume in the first second ≤ 70% or hospitalizations due to pulmonary exacerbation after three years of follow-up.

No significant associations were found between inflammatory markers and colonization by *Pseudomonas aeruginosa* after three years. However, high cytokine concentrations are usually found in

Table 2. Characterization of inflammatory markers at baseline of study among children/adolescents undergoing clinical follow-up at interdisciplinary cystic fibrosis outpatient clinic

Variable	Cystic fibrosis group (n = 38)	Group without cystic fibrosis (n = 31)	P-value
	Median (IQR)	Median (IQR)	
TNF-α (pg/ml)	36.70 (1.63; 63.67)	48.88 (40.18; 58.16)	0.085
IL-1β (pg/ml)	12.55 (8.36; 39.98)	4.43 (2.38; 4.73)	**< 0.001**
MPO (mU/ml)	395.34 (285.42; 488.07)	198.47 (177.95; 199.96)	**< 0.001**
CRP (mg/dl)	4.45 (1.60; 10.09)	2.80 (2.30; 4.60)	0.110
CRP/albumin (mg/dl:g/dl)	1.36 (0.36; 2.77)	0.70 (0.40; 1.10)	0.077

CRP = C-reactive protein; IL-1β = interleukin-1 beta; IQR = interquartile range; MPO = myeloperoxidase; n = absolute number; TNF-α = tumor necrosis factor-alpha. Mann-Whitney test.

Table 1. Clinical and demographic characterization at baseline of study, among children/adolescents undergoing clinical follow-up at interdisciplinary cystic fibrosis outpatient clinic

Variable	Cystic fibrosis group (n = 38)		Group without cystic fibrosis (n = 31)		P-value
		95% CI		95% CI	
Sex[1]					
Male	17 (44.74)	(28.17; 61.30)	12 (38.71)	(20.55; 56.87)	0.614[4]
Female	21 (55.26)	(38.70; 71.82)	19 (61.29)	(43.13; 79.45)	
Age (years)[2]	3.75 (2.71; 7.00)	-	4.62 (3.04; 8.91)	-	0.242[5]
Age at diagnosis (months)[2]	3.50 (2.00; 11.00)	-	-	-	
Mutation[1]					
Delta F508 homozygote	7 (18.42)	(5.51; 31.33)	-	-	-
Delta F508 heterozygote	17 (44.74)	(28.17; 61.30)	-	-	
Other mutation	6 (15.79)	(3.64; 27.93)	-	-	
Not evaluated	8 (21.05)	(7.47; 34.63)	-	-	
Culture from oropharyngeal secretion[1]					
Negative	16 (42.11)	(25.66; 58.55)	12 (100)	-	-
P. aeruginosa	12 (31.58)	(11.65; 40.98)	-	-	
Other*	10 (26.32)	(16.09; 47.06)	-	-	
Nutritional status[1]					
Acceptable (> 25th percentile)	22 (57.89)	(41.44; 74.34)	-	-	-
At risk	11 (28.95)	(13.84; 44.05)	-	-	
Nutritional failure	5 (13.16)	(1.89; 24.41)	-	-	
Nutritional status (W/L or BMI/A)[1†]					
< 50th percentile	25 (65.79)	(49.99; 81.59)	12 (38.71)	(22.70; 57.59)	**0.025**[4]
≥ 50th percentile	13 (34.21)	(18.41; 50.01)	19 (61.29)	(42.41; 77.29)	
FEV1 (%)[3]	76.67 (± 19.90)	(65.64; 87.69)	88.57 (± 10.0)	(82.80; 94.34)	0.054[6]
Pancreatic failure[1]	29 (76.32)	(62.15; 90.47)	-	-	-
Shwachman-Kulczycki score[3]	86.76 (± 17.92)	(80.78; 92.73)	-	-	-

P. aeruginosa = *Pseudomonas aeruginosa*; BMI/A = body mass index-to-age; CI = confidence interval; FEV1 = forced expiratory volume in first second; W/L = weight-to-length; *others = *Staphylococcus aureus* and *Burkholderia cepacia*; †weight-to-length < 2 years of age; body mass index-to-age ≥ 2 years of age; [1]n (%); [2]median (interquartile range); [3]mean (± standard deviation); [4]chi-square; [5]Mann-Whitney; [6]Student t test.

infected cystic fibrosis patients.[27] In a previous study, conducted on 20 adults with cystic fibrosis, those with infection by *Pseudomonas aeruginosa* in association with decreased lung function and presence of systemic inflammatory response, with increased levels of tumor necrosis factor-α and C-reactive protein, experienced chronic episodes of pulmonary exacerbation.[29] Chronic inflammatory diseases can also lead to persistent increases in the serum levels of C-reactive protein.[30] In a cross-sectional study on 58 adults with cystic fibrosis in which the relationship between inflammatory markers in the plasma and both morbidity and the number of hospitalizations was investigated, significant associations with high plasma or serum levels of IL-6, interleukin-1β and C-reactive protein were found.[31]

Pseudomonas aeruginosa is one of the most prevalent microorganisms isolated in patients with cystic fibrosis. Once established, *Pseudomonas aeruginosa* infections are difficult to eradicate and have been associated with declines in lung function. Therefore, aggressive antibiotic therapy is recommended as an eradication protocol, and this is usually successful.[32] Although C-reactive protein levels usually decrease from the beginning to the end of the eradication protocol,[33] the present study (in which inflammatory markers were evaluated at the baseline) showed that the C-reactive protein/albumin ratio was associated with forced expiratory volume in the first second ≤ 70% after three years of follow-up. This indicates that higher levels of C-reactive protein and/or lower levels of albumin were present even in children/adolescents with *Pseudomonas aeruginosa* colonization who were being treated using eradication protocols.

C-reactive protein has biological relevance since its serum levels increase within six hours in response to infection and/or inflammation, and its circulating levels decrease rapidly when the stimulus is removed.[26] Albumin levels are associated with the chronic nature of diseases, and represent the inflammatory status. However, evaluation of this marker alone can create bias because albumin levels are affected by poor nutritional and chronic inflammatory status.[7] Therefore, higher levels of C-reactive protein generally suggest an acute infectious or inflammatory process, whereas low albumin is more frequently associated with chronic diseases and is often associated with nutritional deficiency.[34] Use of these markers is feasible because they are readily measured in serum. Facilities for automated assays are available in most clinical laboratories and these markers are often determined during hospital-based follow-ups.[26] Thus, the combination of C-reactive protein and albumin allows evaluation of an inflammatory-nutritional factor, and the C-reactive protein/albumin ratio may be an indicator of a stronger inflammatory response.[7] In the present investigation, a significant association was found between the C-reactive protein/albumin ratio and forced expiratory volume in the first second ≤ 70% after three years of follow-up. There is a lack of studies evaluating the C-reactive protein/albumin ratio among children/adolescents with cystic fibrosis. In a study on 334 adults with severe sepsis or septic shock, it was concluded that the C-reactive protein/albumin ratio at the time of discharge from the intensive care unit was correlated with the long-term prognosis (up to 90 days) after an episode of sepsis.[35]

The present study had certain limitations. The sample size was defined using a non-probabilistic convenience method, and this has limitations, since the results cannot be extrapolated to the population. The study had a small sample size and the evaluation

Table 3. Bivariate association between inflammatory markers at baseline of study and clinical outcomes after three years of follow-up among children/adolescents at an interdisciplinary cystic fibrosis outpatient clinic

Variables	FEV1 ≤ 70 %		Hospitalization		Positive culture for *Pseudomonas aeruginosa*		BMI/A < 50th percentile	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
TNF-α (pg/ml)								
Adequate	1.00	0.952	1.00	0.437	1.00	NA	1.00	0.459
High	1.08 (0.08; 14.41)		1.89 (0.38; 9.39)		-		0.53 (0.10; 2.88)	
IL-1β (pg/ml)								
Adequate	1.00	0.297	1.00	0.689	1.00	0.094	1.00	0.942
High	0.37 (0.06; 2.37)		0.75 (0.18; 3.13)		0.20 (0.03; 1.31)		1.06 (0.21; 5.37)	
MPO (mU/ml)								
Adequate	1.00	0.571	1.00	0.631	1.00	NA	1.00	0.329
High	0.43 (0.02; 8.04)		0.60 (0.07; 4.83)		-		2.87 (0.34; 23.92)	
CRP (mg/dl)								
Adequate	1.00	0.250	1.00	0.912	1.00	0.760	1.00	0.393
High	2.93 (0.47; 18.33)		0.93 (0.23; 3.64)		0.75 (0.12; 4.76)		1.96 (0.42; 9.10)	
CRP/albumin (mg/dl:g/dl)								
Adequate	1.00	**0.018**	1.00	0.314	1.00	0.652	1.00	0.393
High	18.00 (1.63; 198.51)		2.00 (0.52; 7.70)		0.65 (0.10; 4.14)		1.96 (0.42; 9.10)	

BMI/A = body mass index-to-age; CI = confidence interval; CRP = C-reactive protein; FEV1 = forced expiratory volume in first second; IL-1β = interleukin-1 beta; MPO = myeloperoxidase; NA = not applicable; OR = odds ratio; TNF-α = tumor necrosis factor-alpha. Fisher's exact test.

on lung function decreased the sample size because this evaluation can only be performed on children aged six years and over.

Moreover, there was no preexisting cutoff point for the inflammatory markers and the systemic markers used may not have reflected pulmonary changes, thereby leading to underestimation of the results. However, the subjects were recruited at a reference center for treatment of cystic fibrosis in the state of Santa Catarina, Brazil, and therefore this sample represents the children/adolescents with cystic fibrosis in the state of Santa Catarina. A cutoff point for the inflammatory markers was established based on a healthy group without cystic fibrosis and, although this group without cystic fibrosis was not matched for sex and age with the cystic fibrosis group, we believe that the serum concentrations of the inflammatory markers were not influenced by the lack of matching between the groups.

No previous studies in which the C-reactive protein/albumin ratio was evaluated among children/adolescents with cystic fibrosis were found, although determination of C-reactive protein and albumin levels forms part of routine hospital evaluations. Multicenter studies need to be conducted in order to evaluate the applicability of the C-reactive protein/albumin ratio among children/adolescents with cystic fibrosis in clinical practice.

CONCLUSION

In the present study, there was no association between inflammatory markers with nutritional status and morbidity. A high C-reactive protein/albumin ratio was associated with forced expiratory volume in the first second ≤ 70% after three years of follow-up. Studies with larger sample sizes are necessary in order to better explore this association.

REFERENCES

1. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-31.
2. Strausbaugh SD, Davis PB. Cystic fibrosis: a review of epidemiology and pathobiology. Clin Chest Med. 2007;28(2):279-88.
3. Nichols D, Chmiel J, Berger M. Chronic inflammation in the cystic fibrosis lung: alterations in inter- and intracellular signaling. Clin Rev Allergy Immunol. 2008;34(2):146-62.
4. Maitra R, Porter MA, Huang S, Gilmour BP. Inhibition of NFkappaB by the natural product Withaferin A in cellular models of Cystic Fibrosis inflammation. J Inflamm (Lond). 2009;6:15.
5. Kim PK, Deutschman CS. Inflammatory responses and mediators. Surg Clin North Am. 2000;80(3):885-94.
6. Matouk E, Nguyen D, Benedetti A, et al. C-Reactive Protein in Stable Cystic Fibrosis: An Additional Indicator of Clinical Disease Activity and Risk of Future Pulmonary Exacerbations. J Pulm Respir Med. 2016;6(5):1000375.
7. Kim MH, Ahn JY, Song JE, et al. The C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Patients with Severe Sepsis or Septic Shock Treated with Early Goal-Directed Therapy. PLoS One. 2015;10(7):e0132109.
8. Alicandro G, Bisogno A, Battezzati A, et al. Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis. J Cyst Fibros. 2014;13(3):328-34.
9. Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax. 2001;56(10):746-50.
10. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr. 1998;132(4):589-95.
11. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-7.
12. World Health Organization. Expert Committee on Physical Status: the use and interpretation of Anthropometry Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. WHO technical report series, 854. Geneva: World Health Organization; 1995. Available from: http://apps.who.int/iris/bitstream/10665/37003/1/WHO_TRS_854.pdf. Accessed in 2017 (Sep 19).
13. Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. J Pediatr. 2009;155(6 Suppl):S106-16.
14. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008;108(5):832-9.
15. Jat KR. Spirometry in children. Prim Care Respir J. 2013;22(2):221-9.
16. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.
17. Gilligan PH, Kiska DL, Appleman MD. Cystic Fibrosis Microbiology. Cumitech 43. Washington: ASM Press; 2006.
18. McPherson RA, Pincus MR. Henry's: clinical diagnosis and management by laboratory methods. 21st ed. Philadelphia: Saunders Elsevier; 2006.
19. Pereira LC, Moreira EA, Bennemann GD, et al. Influence of inflammatory response, infection, and pulmonary function in cystic fibrosis. Life Sci. 2014;109(1):30-6.
20. Rao TS, Currie JL, Shaffer AF, Isakson PC. Comparative evaluation of arachidonic acid (AA)- and tetradecanoylphorbol acetate (TPA)-induced dermal inflammation. Inflammation. 1993;17(6):723-41.
21. Dumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromocresol green. 1971. Clin Chim Acta. 1997;258(1):21-30.
22. Xie Q, Zhou Y, Xu Z, et al. The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. BMC Nephrol. 2011;12:30.
23. Bilton D, Canny G, Conway S, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. J Cyst Fibros. 2011;10 Suppl 2:S79-81.

24. Shwachman H, Kulczycki LL. Long-term study of one hundred five patients with cystic fibrosis; studies made over a five- to fourteen-year period. AMA J Dis Child. 1958;96(1):6-15.
25. Stephenson AL, Mannik LA, Walsh S, et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. Am J Clin Nutr. 2013;97(4):872-7.
26. Shoki AH, Mayer-Hamblett N, Wilcox PG, Sin DD, Quon BS. Systematic review of blood biomarkers in cystic fibrosis pulmonary exacerbations. Chest. 2013;144(5):1659-70.
27. Hansen CR, Pressler T, Nielsen KG, et al. Inflammation in Achromobacter xylosoxidans infected cystic fibrosis patients. J Cyst Fibros. 2010;9(1):51-8.
28. Sagel SD, Wagner BD, Anthony MM, Emmett P, Zemanick ET. Sputum biomarkers of inflammation and lung function decline in children with cystic fibrosis. Am J Respir Crit Care Med. 2012;186(9):857-65.
29. Jones AM, Martin L, Bright-Thomas RJ, et al. Inflammatory markers in cystic fibrosis patients with transmissible Pseudomonas aeruginosa. Eur Respir J. 2003;22(3):503-6.
30. Gomes de Lima KV, Maio R. Nutritional status, systemic inflammation and prognosis of patients with gastrointestinal cancer. Nutr Hosp. 2012;27(3):707-14.
31. Ngan DA, Wilcox PG, Aldaabil M, et al. The relationship of systemic inflammation to prior hospitalization in adult patients with cystic fibrosis. BMC Pulm Med. 2012;12:3.
32. Ramsay KA, Sandhu H, Geake JB, et al. The changing prevalence of pulmonary infection in adults with cystic fibrosis: A longitudinal analysis. J Cyst Fibros. 2017;16(1):70-77.
33. Sharma A, Kirkpatrick G, Chen V, et al. Clinical utility of C-reactive protein to predict treatment response during cystic fibrosis pulmonary exacerbations. PLoS One. 2017;12(2):e0171229.
34. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond). 2009;9(1):30-3.
35. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3):e59321.

Acknowledgements: The authors thank all the children/adolescents and their parents/guardians who agreed to participate in the study. This work was supported by the Brazilian National Council for Scientific and Technological Development (CNPq)

Sources of Funding: This study received a research grant from the Brazilian National Council for Scientific and Technological Development (CNPq) [grant number #474945/2008-1]

Conflict of interest: None

Date of first submission: April 12, 2017
Last received: August 22, 2017
Accepted: September 10, 2017

Address for correspondence:
Yara Maria Franco Moreno
Universidade Federal de Santa Catarina (UFSC), Centro de Ciências da Saúde, Campus Universitário
Rua Roberto Sampaio Gonzaga, s/nº
Florianópolis (SC) — Brasil
CEP 88040-900
Fax. (+55 48) 3721-9542
Tel. (+55 48) 3721-2215
E-mail: yara.moreno@ufsc.br

Epidemiological situation of acquired immunodeficiency syndrome (AIDS)-related mortality in a municipality in northeastern Brazil. A retrospective cross-sectional study

Luana Rodrigues da Silva[I], Ellen Thallita Hill Araújo[II], Moisés Lopes Carvalho[III], Camila Aparecida Pinheiro Landim Almeida[IV], Adélia Dalva da Silva Oliveira[V], Patrícia Maria Gomes de Carvalho[VI], Tatyanne Silva Rodrigues[VII], Viriato Campelo[VIII]

Centro Universitário UNINOVAFAPI, Teresina (PI), Brazil

[I]RN. Nurse, Undergraduate Nursing Department, Centro Universitário UNINOVAFAPI, Teresina (PI), Brazil.

[II]RN. Master's Student, Department of Business Sciences, Fundação Sousândrade, Universidade Atlântica, São Luís (MA), Brazil.

[III]RN. Doctoral Student, Department of Biochemistry and Photodynamic Therapy Applied to Biomedical Engineering, Universidade do Vale do Paraíba (UNIVAP), São José dos Campos (SP), Brazil.

[IV]RN, MSc, PhD. Titular Professor, Master's Program on Family Health, Centro Universitário UNINOVAFAPI, Teresina (PI), Brazil.
orcid.org/0000-0003-4843-4572

[V]RN, MSc, PhD. Coordinator, Undergraduate Nursing Department, Centro Universitário UNINOVAFAPI, Teresina (PI), Brazil.

[VI]RN, MSc, PhD. Coordinator, Undergraduate Nursing Department, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.

[VII]RN. Master's Student, Postgraduate Program on Nursing, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.

[VIII]MD, MSc, PhD. Coordinator, Master's Program on Science and Health, Universidade Federal do Piauí (UFPI), and Physician at the Court of Justice of the State of Piauí (TJ/PI), Teresina (PI), Brazil.

KEY WORDS:
Epidemiology.
Mortality.
Acquired immunodeficiency syndrome.
Health information systems.
Brazil.

ABSTRACT

CONTEXT AND OBJECTIVE: The number of acquired immunodeficiency syndrome (AIDS)-related deaths covers different segments of the population differently, making monitoring of this mortality essential. The aim of this study was to describe the epidemiological situation of AIDS-related mortality in a municipality in the northeastern region of Brazil.

DESIGN AND SETTING: Retrospective cross-sectional study based on data from death certificates in the mortality information system of the Health Information Center, Municipal Health Foundation, Brazil.

METHODS: Between 2003 and 2013, we investigated death certificates on which AIDS-related mortality was reported. Sociodemographic data, year, place, type of establishment where death occurred and underlying and associated causes that led to AIDS-related death were described. The Mann-Kendall test was used to verify the growth trend of the standardized mortality rate over the period studied.

RESULTS: Among the 1,066 AIDS-related deaths, 69.7% were among men; 47.2% of the individuals were 28-41 years of age, 32.7% had had 4-7 years of schooling, 66.9% were *pardos* (mixed race), 55.7% were unmarried and 15.3% were housekeepers. Hospitals were the site of 97% of the deaths, and 91% occurred at public hospitals. Respiratory failure was the main cause of death. The prevalence of infectious and parasitic diseases was 99.0%. AIDS-related mortality increased by 160% over the period studied, from 5.5/100,000 inhabitants in 2003 to 14.3/100,000 in 2013.

CONCLUSION: In the Brazilian municipality studied here, AIDS-related mortality was most prevalent among men and young adults of lower socioeconomic level. Over the period studied, the mortality rate increased.

INTRODUCTION

The high number of deaths due to acquired immunodeficiency syndrome (AIDS) in different segments of the Brazilian population has been studied within several fields of science. It is very important to gain knowledge of the underlying circumstances and causes of this infectious disease. However, its high mortality rate represents a constant challenge within healthcare professionals' practice and for the healthcare system. Such challenges may reflect institutional, professional and personal changes.

AIDS is an infectious disease caused by the human immunodeficiency virus (HIV), which affects the immune system and gives rise to immunosuppression, with T-CD4+ lymphocyte deficiency and dysfunction and impairment of the cellular immune response.[1] This infection has a large social dimension because of the large number of people infected with HIV. By the end of 2015, worldwide, 38.8 million people were living with HIV.[2] In 2010, Brazil had 630,000 people with the virus, which resulted in 34,500 new AIDS infections each year. Among the virus carriers, 255,000 were unaware that they were carrying HIV.[3,4]

A United Nations report on the worldwide situation showed that, in 2001, there were about 3.4 million new cases of HIV infection. In 2012, about 35.3 million people were living with HIV, with a significant increase in the number of cases of infection. At the same time, the number of AIDS-related deaths was declining, such that there were 1.2 million deaths in 2014.[3]

According to data from the Brazilian Ministry of Health's Department of Sexually Transmissible Diseases (STDs), AIDS and Viral Hepatitis, the state of Piauí, located in the northeastern region, had an AIDS mortality coefficient of 2.4/100,000 inhabitants (2007-2013), which was lower than the AIDS-related mortality rate for Brazil (5.6/100,000 inhabitants). These data suggest that AIDS epidemiology and mortality span different segments of the population in different manners.

Thus, epidemiological studies have emphasized the importance of caring for HIV/AIDS patients through provision of antiretroviral drugs at healthcare services.[5]

Universal access to antiretroviral therapy became available in Brazil in 1991 through use of zidovudine monotherapy (AZT). In 1996, highly active antiretroviral therapy was introduced with a combination of three drugs. By 2006, more than 16 drugs were available for treating AIDS in Brazil.[6] Antiretroviral therapy is started when the levels of defense cells (T-CD4+ lymphocytes) are below 350 cells/mm^3, or when patients have some symptoms, with or without opportunistic infections.[7]

Because of the difficulty of regularly obtaining comprehensive, reliable and comparable mortality data, the Ministry of Health implemented a national epidemiological surveillance system and a single death certificate (DC) model in 1975. These measures resulted in establishment of the Mortality Information System (SIM/MS), which is responsible for compiling data on deaths that occur throughout the national territory, thus enabling construction of demographic and health indicators for the population.[8,9]

In this context, the present research was justified by the high number of AIDS-related deaths in different segments of the population and the importance of determining the circumstances and the underlying and associated causes. Moreover, given the lack of scientific studies on the epidemiological situation of AIDS-related mortality in the northeastern region of Brazil and, more specifically, in the municipality of Teresina, state of Piauí, monitoring of these deaths becomes essential.

OBJECTIVE

The objective of this study was to describe the epidemiological situation of AIDS-related mortality in the municipality of Teresina, located in the northeastern region of Brazil, using unified data from death certificates stored in the Mortality Information System.

METHODS

This was a cross-sectional, quantitative, descriptive and retrospective study. It used data on mortality due to AIDS in the municipality of Teresina that was available in the SIM. The information was gathered at the Health Information Center of the Municipal Health Foundation (NUINSA-FMS) in the city of Teresina, Brazil. There was good data coverage and satisfactory data quality.

Teresina, the capital of the state of Piauí, is in the central-western part of the state and the mid-northern part of the northeastern region of Brazil. It has an area of approximately 1,756 km^2. The population was 814,230 (380,612 men, 40.6%, and 433,618 women, 59.4% in 2010), with 767,557 people living in the urban area and 46,673 inhabitants in the rural area.[10]

The inclusion criteria for selecting the cases were that they needed to be AIDS-related deaths reported in the SIM between 2003 and 2013, which occurred in the city of Teresina. Data collection took place in September 2014, using a form constructed according to data contained in death certificates, which are also available in the SIM. The study variables were sociodemographic characteristics (gender, age, schooling, marital status, race/color and occupation) location and type of establishment (public or private institution) where deaths occurred, year of death and causes that led to death from AIDS.

The results were organized through insertion of data into the Excel software. The data were presented in the form of absolute numbers (N), relative frequencies (%) and graphs containing information on sociodemographic characterization and description of the underlying causes of death from AIDS. Mortality coefficients were constructed using the number of AIDS-related deaths in the municipality of Teresina and the year, and these data were obtained from the SIM/MS. The specific coefficients of AIDS-related mortality per 100,000 inhabitants were calculated considering the population living in Teresina, Brazil. All data collected were processed in the Statistical Package for the Social Sciences (SPSS) software, version 21.0. The Mann-Kendall test was used to ascertain the growth trend of the standardized mortality rate over the period studied.

This project was implemented after approval was received from the Research Ethics Committee of the UNINOVAFAPI University Center, Teresina, Piauí, Brazil, through ethics approval certificate (CAAE) no. 34750114.5.0000.5210 and report no. 771 803, in August 2014.

RESULTS

Among the 1,066 deaths due to AIDS in Teresina between 2003 and 2013, the highest numbers of cases occurred among men (69.7%) and among people aged 28-41 (47.2%). Although the high rate of unknown data (21%) hampered the analysis on schooling, the majority (32.7%) of the people for whom this was recorded had attended school for 4 to 7 years (complete elementary schooling). In relation to marital status, there was a higher prevalence of unmarried people (55.7%). The race or color informed by the relatives was *pardo* (mixed) in 66.9% of the cases (**Table 1**). **Figure 1** shows the distribution of deaths according to the type of occupation or activity performed.

Regarding the place where the AIDS-related deaths occurred, among the 1,066 deaths analyzed, 1,034 (97%) occurred at hospitals, 23 (2.2%) at home, six (0.6%) in an unknown place, two in other places (0.2%) and one (0.1%) at healthcare facilities other than hospitals (0.1%). Regarding the type of establishment where the deaths occurred, public institutions were most prevalent, with 970 (91%) of the deaths.

Table 2 shows the distribution of the underlying causes of AIDS-related deaths reported to the SIM over the period studied.

Respiratory failure (35.6%) was the largest cause of death. AIDS was in fifth place, with 5.2% of the deaths.

Regarding the causes associated with AIDS-related mortality in Teresina during the period studied, the distribution of the deaths according to the chapters of the Tenth Edition of the International Classification of Diseases and Causes of Death (ICD-10) was as follows (considering that more than one associated cause could be informed for the same death): for 1,030 deaths (99.0%), the associated causes were in Chapter I, relating to infectious and parasitic diseases; for 271 deaths (26.1%), the causes were in Chapter X, respiratory tract; for 42 deaths (4%), the causes were in Chapter XI, digestive tract; and for 35 deaths (3.4%), the causes were in Chapter IV, endocrine, nutritional and metabolic diseases. Other, less frequently associated causes were diseases of the genitourinary system (Chapter XIV), for 32 deaths (3.1%); diseases of the nervous system (Chapter VI), for 30 deaths (2.9%); and diseases of the circulatory system (Chapter IX), for 21 deaths (2.0%).

Regarding the AIDS-related mortality rate, there was an increase of 160% over the period studied, from 5.5 deaths/100,000 inhabitants in 2003 to 14.3/100,000 in 2013. Over the years analyzed, three times stood out: the year 2012, with the greatest significance, followed by 2009 and 2013. The series showed a progressive increase in mortality rates, as demonstrated by the Mann-Kendall test result (P = 0.032) and by the trend line, which confirmed that this rate will tend to increase over the coming years (**Figure 2**).

Table 1. Sociodemographic characterization of the epidemiological situation of acquired immunodeficiency syndrome (AIDS)-related mortality in Teresina (PI), Brazil, 2003 to 2013 (n = 1066)

Variable	n	%
Gender		
Male	744	69.7
Female	308	29.0
Unknown	14	1.3
Age group (years)		
0-13	23	2.2
14-27	152	14.3
28-41	504	47.2
42-55	293	27.5
56-69	76	7.1
70 and over	6	0.6
Unknown	12	1.1
Schooling (years)		
None (illiterate)	72	6.7
1-3 (incomplete elementary education)	207	19.4
4-7 (completed elementary education)	350	32.7
8-11 (completed high school)	173	16.2
12 or more (tertiary education)	43	4.0
Unknown	221	21.0
Marital status		
Unmarried	583	55.7
Married	280	26.3
Widowed	50	4.8
Judicially separated/divorced	37	3.5
Unknown	116	9.7
Race/color		
White	111	10.4
Black	129	12.1
Asian	1	0.1
Pardo (mixed)	714	66.9
Indigenous	2	0.2
Unknown	109	10.3

Source of data: Health Information Center of the Municipal Health Foundation (NUINSA-FMS), Teresina (PI), Brazil.

DISCUSSION

The profile of AIDS-related deaths in Teresina over the period studied corroborated the findings from previous studies, which reported that the population with HIV/AIDS consisted predominantly of adult men with no stable partner who had not completed high school.[11]

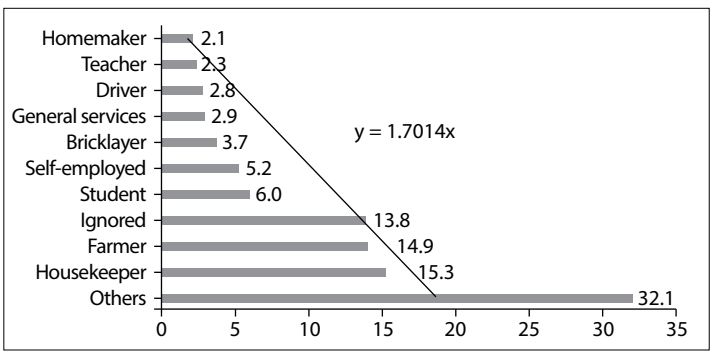


Figure 1. Occupations of the individuals who died due to the acquired immunodeficiency syndrome (AIDS) in Teresina (PI), Brazil, 2003 to 2013 (n = 1066).

Table 2. Description of the underlying causes of death among acquired immunodeficiency syndrome (AIDS)-related deaths reported in Teresina (PI), Brazil, 2003 to 2013 (n = 1066)

Underlying cause of death	n	%
Respiratory insufficiency	380	35.6
Cardiorespiratory arrest	121	11.4
Multiple organ failure	94	8.8
Acute respiratory insufficiency	69	6.5
AIDS	55	5.2
Septic shock	35	3.3
Sepsis	35	3.3
Neurotoxoplasmosis	31	2.9
Pneumonia	28	2.6
Pneumocystosis	24	2.3
Hypovolemic shock	12	1.1
Others	182	17.1

Source of data: Health Information Center of the Municipal Health Foundation (NUINSA-FMS), Teresina (PI), Brazil.

According to the Ministry of Health, the coefficient of AIDS-related mortality among men is higher than among women: 8.4 and 4.2 deaths per 100,000 inhabitants, respectively.[12] Another study confirmed that there was higher mortality among men than among women, with general ratios of 2.5 for the coefficients and 2.4 for the number of deaths. Likewise, that study showed that the population studied consisted predominantly of men (69.7%).[13] This differed from more recent studies that have reported that the AIDS epidemic and mortality have become feminized.[14,15]

Women account for almost half of the 40.3 million people who have died due to HIV or AIDS worldwide. In Brazil, the numbers of AIDS cases among women have been increasing, in comparison with the number among men. Thus, the mortality rate due to AIDS among men has shown a more significant decrease than the rate among women.[16]

In relation to age group, the mortality rate among older adults and elderly people aged 56 to 69 years was 7.1%), while among elderly people aged 70 years and over, it was 0.6%. This demonstrates that deaths due to AIDS among elderly people were significantly frequent. A previous study carried out in Teresina, which investigated the epidemiological characteristics of the incidence of elderly people with AIDS, identified higher prevalence among elderly people aged between 60 and 69 years (88.5%).[17]

Other studies have considered schooling to be one of the main socioeconomic indicators negatively correlated with increased AIDS incidence and mortality, i.e. lower schooling would be linked to higher incidence and mortality. In this respect, the category of schooling with the highest number of deaths in the present study was that of 4 to 7 years of education (incomplete elementary school), which was concordant with other reports.[2-18]

Since the beginning of the 1990s, cases of AIDS-related mortality have become more frequent among individuals with lower educational levels. AIDS-related mortality in the years 2001 and 2010 occurred more among individuals with 4 to 7 years of schooling, thus confirming the results from the present study.[19] One explanation for this observation is that the greater that individuals' education level is, the greater their knowledge about AIDS will be, which provides them with better social resources to live with the disease.[20]

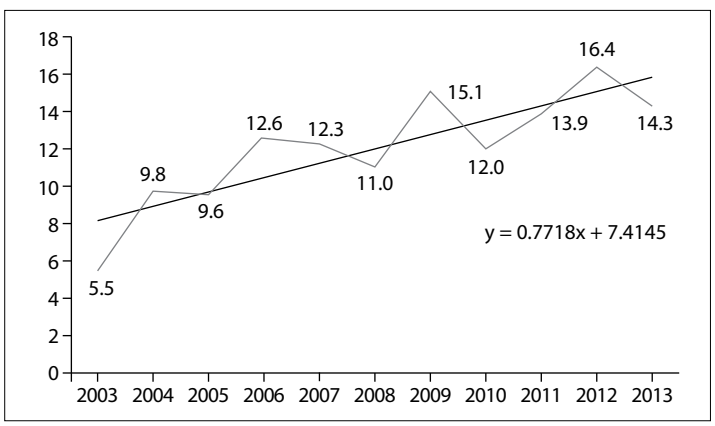


Figure 2. Standardized crude mortality rate for AIDS-related mortality in Teresina (PI), Brazil, 2003 to 2013 (n = 1066)

One important issue that needs to be addressed is the large number of records with no information about schooling (21% of the 1,066 deaths examined here). Information that is missing from death certificates is a problem faced by the epidemiological surveillance system. The main underreporting problem is that information is incomplete, especially regarding sociodemographic information, which restricts wider use of death certificates.

Concerning marital situation, AIDS-related mortality was most prevalent among unmarried people (55.7%). Research on the epidemiological profile of AIDS in Caruaru, state of Pernambuco, also reported that AIDS-related mortality was most prevalent among unmarried people (69.2%), followed by deaths among those who were married (21.2%), separated (3.8%) and widowed (2.9%). One of the theories for elucidating the high AIDS mortality rate among unmarried people is that they have a greater number of sexual partners and more frequently have unprotected sex and, thus, have greater chances of contracting the infection.[21] With regard to married women, there is evidence showing that they face difficulty in asking their husband to use a condom, since these women are expected to trust him and not raise suspicion about his fidelity.[22]

In the present population, the largest racial group was *pardos* (66.9%), followed by blacks (12.1%) and whites (10.4%). These results differed from those of an analysis on race/color, on data in the health information systems of the Brazilian National Health System (Sistema Único de Saúde, SUS) for the city of São Paulo. According to that analysis, the distribution of deaths in this regard was stable, such that white race/color accounted for around 70.5% of AIDS-related deaths in 2010 in the city of São Paulo, while blacks accounted for 23.1% of these deaths in the same year.[23]

An epidemiological study conducted in the state of Santa Catarina showed that most patients who died from AIDS were white, followed by blacks.[24] In a study conducted by the Ministry of Health, individuals with white skin color accounted for 52.1% of AIDS cases in Brazil, while 36.9% were *pardo* and 10.3% were black.[9] In comparing the studies, there was a difference that could be explained by the predominance of white individuals who were the descendants of European immigrants in Santa Catarina.

Another variable analyzed was occupation, for which, like schooling, there was also a significant proportion of unknown data (13.8%). The results highlighted highest prevalences of housekeepers (15.3%) and farmers (14%). People living with HIV/AIDS who are housekeepers may have abandoned their jobs to hide their condition, while continuing to work at home, taking care of spouses and children.[25]

The result relating to the place of death shows that, among the establishments included in the survey, hospitals had the highest death rate (97% of the cases). This response is in line with previously published studies, which have reported that in most cases, people with HIV/AIDS only seek healthcare institutions after developing some type of opportunistic disease.[26,27] In addition, public healthcare institutions predominated, accounting for 91% of deaths. These numbers reflect the change in the epidemiological situation regarding AIDS that has taken place: individuals of high socioeconomic level characterized the beginning of the epidemic; subsequently, the disease spread, such that it now mainly affects those with low income.[11]

The results showed that AIDS was the main underlying cause of death in only 5.2% of the cases. This trend was also observed in a study conducted in the state of Amazonas on 129 AIDS patients who died and were subjected to necropsy. In that study, the most frequent cause of death was tuberculosis, accounting for 28%.[28] Use of the concept of the underlying cause of death is essential for analysis on historical trends, for comparisons between countries and for common use for standardized procedures to guide prevention of death.[29] Respiratory insufficiency was seen to be highly prevalent among the individuals assessed in this study, affecting a total of 35.6%. A study carried out in the state of Ceará revealed that respiratory failure was the main complication (56%) among patients with AIDS, and it was a fundamental factor leading to the outcome of death, even during hospitalization (32.8%).[30]

Analysis on the distribution of deaths through the codes of causes described in the International Classification of Diseases, 10th revision (ICD-10), made it possible to identify a higher rate of infectious and parasitic diseases. The group of respiratory diseases was the second largest group in importance as associated causes of death. Another study in Teresina also showed that infectious and parasitic diseases were the main causes associated with deaths AIDS-related deaths, in this city, followed by pulmonary diseases.[31]

A study carried out in São Paulo showed that AIDS was the cause of 65.3% of the deaths investigated. Among these, tuberculosis was mentioned as the main associated cause; the progression of the disease was worsened by tuberculosis, which doubled the risk of death.[32] Another study carried out in the state of São Paulo on AIDS-related deaths that occurred in that state observed that the respiratory diseases group was in second place among the associated causes of death.[13] Regarding pulmonary infections due to AIDS, a third study pointed out that 85% of the patients died with a low T-CD4+ count, and that pneumonia was the main associated cause.[33]

With regard to the AIDS-related mortality rate, the analysis of the present study showed that, over the period from 2003 to 2013, in Teresina, the number of deaths increased by 160%. In the first year surveyed, the rate was equivalent to 5.5 deaths/100,000 inhabitants, whereas it was 14.3 in the last year. Despite the implementation of specific healthcare policies for individuals living with HIV/AIDS and use of antiretroviral therapy, this study showed that there is a trend towards growing numbers of cases of AIDS-related deaths in Teresina.

A study carried out at a referral hospital for transmitted diseases in Piauí, located in Teresina, revealed that the numbers of reports of AIDS in municipalities with less than 50,000 inhabitants are increasing. This indicates that the mortality rate will be increasing.[17] Brazilian research bodies have been encouraging development of further scientific studies on the epidemiological characteristics of individuals living with infectious diseases,[34] with the objective of increasing the visibility of the Brazilian public healthcare system for investing in prevention and control strategies.

Through the results presented and discussed in this study, it is possible to consider that AIDS-related mortality has reached heterogeneously different segments of the population studied, and that even with implementation of antiretroviral therapy, the mortality rate due to the disease is still increasing. Knowledge of the epidemiological situation of individuals who died due to AIDS-related conditions is necessary for planning and evaluating healthcare. In this regard, the findings from the present study not only provide support for elaboration of new healthcare policies but also make it possible to improve the quality of the care given to these individuals and furnish scientific support for future studies.

The limitations of this study were its cross-sectional design and its use of information from death certificates obtained from public databases, considering that under-registration of information exists, as observed for the variables of gender, age, schooling, marital status and race/color. However, in view of the magnitude of the topic of this research, obtaining the results from other sources was not possible.

CONCLUSION

AIDS-related mortality in the Brazilian municipality studied here was most prevalent among men and among young adults of lower socioeconomic level. Furthermore, the mortality rate increased over the period studied. In this light, this study may constitute a basis for elaborating new healthcare policies and for improving the quality of the care provided to these individuals. One suggestion would be to focus investments on infection prevention and control strategies and to elaborate new studies in order to broaden the scientific knowledge relating to this subject.

REFERENCES

1. Carpes JS, Lobo E, Pereira J. Morbidade e Mortalidade por HIV/Aids em Florianópolis: desafio para a gestão. Coleção Gestão Saúde Pública. 2013;8(1):112-23. Available from: http://gsp.cursoscad.ufsc.br/wp/wp-content/uploads/2013/03/Artigo_06.pdf. Accessed in 2017 (Sep 25).

2. GBD 2015 HIV Collaborators, Wang H, Wolock TM, et al. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. Lancet HIV. 2016;3(8):e361-87.
3. On the Fast-Track to end AIDS by 2030: Focus on location and population. Geneva: UNAIDS/WHO; 2015. Available from: http://www.unaids.org/sites/default/files/media_asset/WAD2015_report_en_part01.pdf. Accessed in 2017 (Sep 25).
4. Santos EM, Reis AC, Westman S, Alves RG. Avaliação do grau de implantação do programa de controle da transmissão vertical do HIV em maternidades do "Projeto Nascer" [Implementation evaluation of Brazil's national vertical HIV transmission control program in maternity clinics participating in the "Nascer" Project]. Epidemiol Serv Saúde. 2010;19(3):257-69.
5. Costa Oliveira MT. O diagnóstico tardio e óbito por aids de pacientes internados em 2005 em um hospital de referência para doenças infecciosas em Belo Horizonte, Minas Gerais [thesis]. Belo Horizonte: Universidade Federal de Minas Gerais; 2007.
6. Lorscheider JA. Geronimo K, Colacite J. Estudo da adesão à terapia antirretroviral para HIV/Aids de pacientes atendidos no município de Toledo/PR. Acta Biomedica Brasiliensia. 2012;3(1):41-51. Available from: http://www.actabiomedica.com.br/index.php/acta/article/view/35/133. Accessed in 2017 (Sep 25).
7. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo clínico e diretrizes terapêuticas para manejo da infecção pelo HIV em adultos. Brasília: Ministério da Saúde; 2013. Available from: http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos. Accessed in 2017 (Sep 25).
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Guia de vigilância epidemiológica. 7ª ed. Brasília: Ministério da Saúde; 2009. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/guia_vigilancia_epidemiologica_7ed.pdf. Accessed in 2017 (Sep 25).
9. Brasil. Ministério da Saúde A experiência brasileira em sistemas de informação em saúde. Brasília: Editora do Ministério da Saúde; 2009. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/experiencia_brasileira_sistemas_saude_volume1.pdf. Accessed in 2017 (Sep 25).
10. Secretaria do Estado da Saúde do Piauí. QualiSUS Rede. Subprojeto Estadual/PI: Região de Saúde Entre Rios/Piauí. Teresina: Secretaria do Estado da Saúde do Piauí; 2012. Available from: http://portalarquivos.saude.gov.br/images/pdf/2014/agosto/08/Subprojeto-QualiSUS-PI-web.pdf. Accessed in 2017 (Sep 25).
11. Lima RR, Santos MJL, Lira MCC, Mangueira SO, Damásio SLC. Perfil epidemiológico da infecção por HIV/AIDS relacionado a atividade ocupacional [Epidemiological profile of HIV/Aids infection related to occupational activity]. Journal of Nursing UFPE On Line. 2015;9(Suppl. 4):8012-8. Available from: http://www.revista.ufpe.br/revistaenfermagem/index.php/revista/article/view/7214/pdf_7885. Accessed in 2017 (Sep 25).
12. Brasil. Ministério da Saúde. Programa Nacional de DST e Aids. Boletim epidemiológico Aids. Ano III - nº 01. Brasília: Ministério da Saúde; 2006. Available from: http://www.aids.gov.br/pt-br/node/82. Accessed in 2017 (Sep 25).
13. Santo AH, Pinheiro CE, Jordani MS. Causas básicas e associadas de morte por AIDS, Estado de São Paulo, Brasil, 1998 [AIDS as underlying and associated causes of death, State of S. Paulo, Brazil, 1998]. Rev Saúde Pública. 2000;34(6):581-8.
14. Pedrosa NL, Paiva SS, Almeida RLF, et al. Série histórica da AIDS no Estado do Ceará, Brasil [The historic data series on AIDS in the state of Ceará, Brazil]. Ciênc Saúde Coletiva. 2015;20(4):1177-84.
15. Almeida ANS, Silveira LC, Silva MRF, Araújo MAM, Guimarães TA. Produção de subjetividade e sexualidade em mulheres vivendo com o HIV/Aids: uma produção sociopoética [Subjectivity and Sexuality Production in Women Living With HIV/Aids: a Sociopoetic Production]. Rev Latino-Am Enfermagem. 2010;18(2):163-9.
16. Costa R, Silva RRA. Fatores relacionados à feminização da epidemia da AIDS: estudo informativo [Factors related to feminization of the epidemy of AIDS: an information study]. Journal of Nursing UFPE On Line. 2013;7(8):5340-4. Available from: http://www.revista.ufpe.br/revistaenfermagem/index.php/revista/article/view/4793/pdf_3269. Accessed in 2017 (Sep 25)
17. Silva HR, Medeiros MOC, Figueiredo TS, Figueiredo MLF. Características clínico-epidemiológicas de pacientes idosos com aids em hospital de referência, Teresina-PI, 1996 a 2009 [Clinical and epidemiological characteristics of elderly patients with AIDS in a reference hospital, Teresina-PI, 1996 to 2009]. Epidemiol Serv Saúde. 2011;20(4):499-507.
18. Silva RAR, Duarte FHS, Nelson ARC, Holanda JRR. Epidemia da Aids no Brasil: Análise do perfil atual. Journal of Nursing UFPE On Line. 2013;7(10):6039-46. Available from: http://www.revista.ufpe.br/revistaenfermagem/index.php/revista/article/view/4882/pdf_3676. Accessed in 2017 (Sep 25).
19. Faqueti A, Rodriguez AMM, Woerner CB, Antonio GD. Perfil epidemiológico de mortalidade por aids na população adulta do Brasil de 2001 a 2010. Revista de Saúde Pública de Santa Catarina. 2014;7(2):29-39. Available from: http://esp.saude.sc.gov.br/sistemas/revista/index.php/inicio/article/view/239/257. Accessed in 2017 (Sep 25).
20. Reis RK, Santos CB, Dantas RAS, Gir E. Qualidade de vida, aspectos sociodemográficos e de sexualidade de pessoas vivendo com HIV/AIDS [Quality of life, sociodemographic factors and sexuality of people living with HIV/AIDS]. Texto Contexto Enferm. 2011;20(3):565-75.
21. Maciel SSSV, Maciel WV, Andrade MC, et al. Perfil epidemiológico da Aids no município de Caruaru-PE [Epidemiological profile of aids in Caruaru City, PE]. Journal of Nursing UFPE On Line. 2010;4(4):1801-7. Available from: https://periodicos.ufpe.br/revistas/revistaenfermagem/article/view/6366/5612. Accessed in 2017 (Sep 26).
22. Silva CM, Vargens OMC. A percepção de mulheres quanto à vulnerabilidade feminina para contrair DST/HIV [Women's perception about female vulnerability to STD and HIV]. Rev Esc Enferm USP. 2009;43(2):401-6.

23. São Paulo. Secretaria da Saúde. Coordenação de Epidemiologia e Informação. Análise do quesito raça/cor a partir de sistemas de informação da Saúde do SUS [Analysis of race/color from the information systems of the Brazilian health system]. (Boletim CEInfo Análise, 5). São Paulo: Secretaria da Saúde; 2011.
24. Schuelter-Trevisol F, Pucci P, Justino AZ, Pucci N, Silva ACB. Perfil epidemiológico dos pacientes com HIV atendidos no sul do Estado de Santa Catarina, Brasil, em 2010 [Epidemiological profile of HIV patients in the southern region of Santa Catarina State in 2010]. Epidemiol Serv Saúde. 2013;22(1):87-94.
25. Bastiani JAN, Padilha MICS, Vieira M, Maliska ICA, Maia ARCR. Pessoas que vivem com HIV/AIDS em Florianópolis/SC, Brasil: ocupação e status socioeconômico ocupacional (1986-2006) [Persons living with HIV/AIDS in Florianópolis/SC, Brazil: occupation and occupational socioeconomic status (1986-2006)]. Rev Eletr Enf. 2012;14(3):579-87.
26. Thuler LCS, Hatherly AL, Góes PN, Silva JRA. Infecção pelo HIV: descritores de mortalidade em pacientes hospitalizados [Mortality descriptors in HIV inpatients]. Rev Saúde Pública. 1998;32(6):572-8.
27. Rezende ELLF. Mortalidade por aids no Brasil [thesis]. Brasília: Universidade de Brasília; 2012.
28. Souza SLS, Feitoza PVS, Araújo JR, Andrade RV, Ferreira LCL. Causas de óbito em pacientes com síndrome da imunodeficiência adquirida, necropsiados na Fundação de Medicina Tropical do Amazonas [Causes of death among patients with acquired immunodeficiency syndrome autopsied at the Tropical Medicine Foundation of Amazonas]. Rev Soc Bras Med Trop. 2008;41(3):247-51.
29. Santo AH. Potencial epidemiológico da utilização das causas múltiplas de morte por meio de suas menções nas declarações de óbito, Brasil, 2003 [Epidemiological potential of multiple-cause-of-death data listed on death certificates, Brazil, 2003]. Rev Panam Salud Pública. 2007;22(3):178-86.
30. Pontes LB, Leitão TMJS, Lima GG, Gerhard ES, Fernandes TA. Características clínico-evolutivas de 134 pacientes com histoplasmose disseminada associada a SIDA no Estado do Ceará [Clinical and evolutionary characteristics of 134 patients with disseminated histoplasmosis associated with AIDS in the State of Ceará]. Rev Soc Bras Med Trop. 2010;43(1):27-31.
31. Campelo V, Gonçalves MAG, Donadi EA. Mortalidade por doenças infecciosas e parasitárias no município de Teresina-PI (Brasil), 1971-2000 [Mortality due to infectious and parasitic diseases in the city of Teresina-PI (Brazil), 1971-2000]. Rev Bras Epidemiol. 2005;8(1):31-40.
32. Santo AH, Pinheiro CE, Jordani MS. Causas múltiplas de morte relacionadas à tuberculose no Estado de São Paulo, 1998 [Multiple-causes-of-death related to tuberculosis in the State of São Paulo, Brazil, 1998]. Rev Saúde Pública. 2003;37(6):714-21.
33. Costa CH. Infecções pulmonares na Aids. Revista Hospital Universitário Pedro Ernesto. 2010;9(2):54-9. Available from: http://revista.hupe.uerj.br/detalhe_artigo.asp?id=161. Accessed in 2017 (Sep 26).
34. Ferraz ML, Yoradjian A, Barbieri A, et al. Epidemiology of acute hepatitis B in a university hospital in São Paulo, Brazil: retrospective study of two five-year periods. Sao Paulo Med J. 1998;116(3):1695-9.

Conflict of interest: None
Sources of funding: None
Date of first submission: May 14, 2017
Last received: September 1, 2017
Accepted: September 10, 2017

Address for correspondence:
Camila Aparecida Pinheiro Landim Almeida
Centro Universitário UNINOVAFAPI, Programa de Mestrado Profissional em Saúde da Família
Rua Vitorino Orthiges Fernandes, 6123, Uruguai
Teresina (PI) — Brasil
CEP 64073-505
Tel. (+55 86) 2106-0723
Fax. (+55 86) 2106-0740
E-mail: camila@uninovafapi.edu.br

DOI: 10.1590/1516-3180.2017.0174100917

Sensory-motor training versus resistance training among patients with knee osteoarthritis: randomized single-blind controlled trial

Aline Bassoli Gomiero[I], Andrea Kayo[II], Marcelo Abraão[I], Maria Stella Peccin[I], Antonio Jose Grande[III], Virginia Fernandes Trevisani[IV]

Universidade de Santo Amaro (UNISA), São Paulo (SP), Brazil

[I]MSc. Physiotherapist, Department of Medicine, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.

[II]PhD. Physiotherapist, Department of Medicine, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.

[III]PhD. Associate Professor, Department of Medicine, Universidade Estadual de Mato Grosso do Sul (UEMS), Campo Grande (MS), Brazil.
orcid.org/0000-0001-7182-075X

[IV]MD, PhD. Associate Professor, Department of Medicine, Universidade Federal de São Paulo (UNIFESP), and Full Professor, Discipline of Reumatology, Universidade de Santo Amaro (UNISA), São Paulo (SP), Brazil.

KEY WORDS:
Osteoarthritis.
Knee.
Exercise.
Pain.
Randomized controlled trial.

ABSTRACT

BACKGROUND: Osteoarthritis of the knee is defined as a progressive disease of the synovial joints and is characterized by failure of joint damage repair. The objective here was to compare the effectiveness of sensory-motor training versus resistance training among patients with knee osteoarthritis.

DESIGN AND SETTING: Randomized, single-blinded controlled trial conducted at the outpatient service of the University of Santo Amaro.

METHODS: A total of 64 patients were randomly assigned to sensory-motor training or resistance training. The evaluations were performed at baseline and 16 weeks after the intervention and included pain evaluation on a visual analogue scale, isometric quadriceps femoris force measurement using a dynamometer, Timed Up and Go test, Tinetti balance scale, Western Ontario and McMaster Universities osteoarthritis index, and the SF-36 quality-of-life questionnaire. Data analysis was performed using analysis of variance with repeated measurements and Cohen's effect size.

RESULTS: Sensory-motor training may be a plausible alternative and showed a small effect on pain and a medium effect on maximal voluntary isometric contraction. Resistance training showed a small effect on balance and a medium effect on mobility.

CONCLUSION: Resistance training and sensory motor training for the lower limbs among patients with knee osteoarthritis seemed to present similar effects on pain and function. However, because there was a considerable risk of type 2 error, further randomized clinical trials are still needed to provide a sound conclusion.

CLINICAL TRIAL REGISTRATION: NCT01529398.

INTRODUCTION

Osteoarthritis of the knee is defined as a progressive disease of the synovial joints and is characterized by failure of joint damage repair subsequent to stress that may have been initiated by an abnormality in any of the articular synovial tissues, including articular cartilage, subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves or synovia. This structural damage results in collapse of the cartilage and subchondral bone, thus leading to symptoms of pain, stiffness and dysfunction.[1-3]

The treatment options for knee osteoarthritis include non-pharmacological, pharmacological or surgical measures. Current clinical guidelines recommend non-pharmacological conservative strategies, including physical exercises, given their ease of application, small number of potential adverse effects and relatively low cost.[3,4]

Because of the large body of evidence demonstrating the beneficial effects of physical exercise among patients with osteoarthritis, exercise is often indicated as one of the main components in the rehabilitation process.[1,3,5-7]

Among the several types of physical exercise programs, muscle strengthening is important because of the relationship between muscle weakness, pain and poor function.[6,8-11] However, traditional strengthening exercises may be insufficient for the subgroup of patients with functional joint instability. One study on this subgroup of patients investigated interventions focusing specifically on symptoms, thus maximizing the effectiveness of the rehabilitation program.[12-14]

As osteoarthritis progresses, sensory-motor skills such as proprioception, static and dynamic balance and neuromuscular control decline because of diminished daily physical exercises and increasing perception of pain. Thus, programs that include agility, coordination and balance (sensory-motor training) may be effective through exposing these individuals to potentially destabilizing loads. This allows the neuromuscular system to adapt to conditions that could induce knee instability during activities of daily living.[3,10,12,15]

In this light, the objective of this study was to compare the effectiveness of sensory-motor training (SMT) versus resistance training (RT) for relieving pain and improving function among a group of individuals with knee osteoarthritis, who were evaluated at the baseline and after 16 weeks of intervention. A secondary objective was to evaluate these individuals' isometric strength, balance and general health.

METHODS

Trial design

This was a randomized single-blind controlled trial that was registered at ClinicalTrials (http://www.clinicaltrials.gov), under protocol number NCT01529398. All participants signed an informed consent form before they were included in the study. All procedures conducted in this study followed international standards for research on human beings, in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Participants

This study was conducted in the physiotherapy sector of the ambulatory of the Interlagos medical specialties outpatient service, which belongs to the University of Santo Amaro (Universidade de Santo Amaro, UNISA) in São Paulo, Brazil. It was conducted between March 2008 and July 2009.

The inclusion criteria were that the patients needed to have a diagnosis of tibiofemoral osteoarthritis that fulfilled the clinical criteria for knee osteoarthritis of the American College of Rheumatology (ACR),[16] 1986; be between 50 and 75 years of age; have not done any physical activity for at least 3 months; and have reached a minimum educational level of 4th grade of elementary education. Participants who presented the following were excluded: uncontrolled arterial hypertension; decompensated diabetes mellitus; decompensated thyroid diseases; cardiorespiratory diseases (ischemia, arrhythmia, precordial pain or physical exercise-induced bronchospasm); liver abnormalities; grade IV functional impairment (Kellgren-Lawrence radiographic scale); or other rheumatic diseases. In addition, patients who needed ambulatory devices and those who were on sick leave from work approved by the government agency for national insurance or presented any other related factor were also excluded.

Interventions

Participants were allocated in a 1:1 ratio to either resistance training or sensory-motor training. Those assigned to the resistance training group received a 16-week exercise program twice a week, which included warm-up on a stationary bicycle for 10 minutes, quadriceps and hamstring strengthening exercises using ankle weights, isometric exercises for the quadriceps muscle (hip flexion with leg extended) and stretching for the lower limbs (stretching of the quadriceps, hamstrings and triceps surae). All physical exercises were performed bilaterally and at a volume of three sets of ten maximal repetitions.

The participants who were allocated to the SMT group received the same warm-up and stretching program as the RT group, with the same duration and frequency of treatment, but with replacement of the strengthening program with a program emphasizing agility, coordination and balance. This program included walking in different directions following verbal commands from the therapist; crossing steps while walking; crossing steps while walking backwards; implementing sudden changes of direction; walking on several types of surfaces (including mattresses); maintaining posture during use of a balance board; and using a mini-trampoline to expose individuals to potentially destabilizing loads.

To ensure linearity within the protocols, only one therapist supervised all the interventions. The groups were composed of four to five patients each, so that it was possible to supervise and monitor all the patients in a safe and effective manner.

In addition to the interventions described above, the two groups had concomitant intervention such as informative talks. They also received an educational program on knee osteoarthritis, which allowed the patients to clarify their doubts and concerns about the disease.

Outcomes

Primary outcomes

Pain was one of the primary outcomes assessed. We used a visual analogue pain scale (VAS) for the participants to report the worst pain that they had felt in their knees over the last 24 hours prior to the evaluation. The VAS is an instrument based on a straight line (100 mm long) graduated from 0 to 100, on which the patient marks the intensity of his/her pain: from zero = no pain to 100 = worst pain imaginable. **Table 1** presents the results from each outcome studied.

Quality of life was assessed by means of the Short Form-36 quality-of-life questionnaire (SF-36). In this, zero points corresponds to the worst quality of life and 100 points corresponds to the best quality of life, as put forward through the questionnaire.[16]

The evaluations were performed at the baseline (T0) and after the end of the physical exercise program (T16).

The other primary outcome was mobility, as measured using the Timed Up and Go (TUG) test. In this test, we measured the time (in seconds) that it took for each individual to stand up from a chair, walk a distance of three meters in a straight line, turn around, walk back and sit down on the chair again.[17] The outcome of mobility involves the individual's gait speed, balance, functional level and ability to stand up, and the risk of falling to which this individual is exposed.

The evaluations were performed at the baseline (T0) and after the end of the physical exercise program (T16).

Secondary outcomes

The isometric strength of the quadriceps muscle (IS) was measured with the subject seated on an extensor chair, with isometric fixation at 45 degrees using a load cell for Miotec traction.

Balance and gait were evaluated through the Tinetti balance assessment tool. This test classifies gait parameters such as speed, step distance, symmetry, standing balance and spin, and also assesses changes to footing that are made while the subject's eyes are closed. The maximum scores are 12 points for gait and 16 points for body balance, thus totaling 28 points.[18]

Functional capacity was measured by means of the Western Ontario and McMaster Universities (WOMAC) index questionnaire. This is specific for patients with knee osteoarthritis and provides information on pain, stiffness and physical function among these individuals. Higher scores indicate greater degree of severity of the disease.

Sample size

The expected difference between the groups was 10%, considering the outcome of mobility, i.e. one point in the TUG test. Thus, a significance level of 5% and a test power of 80% were considered for the sample size calculation. This showed that the ideal sample size would be 46 patients for each group. However, we were only able to recruit 32 patients for each group, and thus the power of the study decreased to 68.3%.

Randomization

The GraphPad Statmate 1.0 software was used to generate randomized numbers. The sequential numbers thus generated through the computerized randomization were then placed in opaque envelopes that were sealed by a physiotherapist who was not involved in the study, thereby keeping the allocation concealed. As the patients underwent their initial assessments, the same physiotherapist assigned the subject to one of the groups based on instructions from the next sealed envelope of the sequence.

Blinding

A second physiotherapist sealed all the envelopes and participated in the evaluations on the study participants. Thus, she was blind to both treatment groups. Regarding the physiotherapist performing the interventions, she could not be blind because of the characteristics of the intervention. Likewise, the participants could not be blind due to the characteristics of the intervention.

Statistical methods

All analyses were performed following the principles of intention-to-treat (ITT) analysis. In case of missing data, we used "last observation carried forward" as the imputation data method. The chi-square test was used to compare the groups regarding the qualitative variables (gender and Kellgren classification), while the descriptive variables were presented as absolute

Table 1. Sensory-motor training versus resistance training among patients with knee osteoarthritis

Variables measured		Group				P* (Interaction effect)	P† (Time [T0 versus T16])	Cohen's d Effect size post-intervention
		SMT ($\bar{x}$)	95% CI	RT ($\bar{x}$)	95% CI			
VAS (score)	T0	6.3	5.47-7.13	6.7	5.80-7.60	0.702	< 0.001	0.24
	T16	4.6	3.84-5.36	4.1	3.16-5.04			
TUG (seconds)	T0	9.1	7.91-10.29	10.5	8.99-12.01	0.395	< 0.001	-0.67
	T16	7.9	7.47-8.33	8.7	7.69-9.71			
MVIC (kilograms)	T0	29.2	25.67-32.73	26.7	23.24-30.16	0.070	0.001	0.55
	T16	39.9	35.61-44.19	33.4	28.35-38.45			
Tinetti (score)	T0	24.3	22.64-25.96	24.1	21.97-26.23	0.832	0.001	- 0.22
	T16	26.0	25.17-26.83	26.5	25.74-27.26			
WOMAC (score)	T0	36.3	29.13-43.47	37.8	31.74-43.86	0.832	0.001	0.09
	T16	30.6	24.25-36.95	29.0	23.27-34.73			

SMT = sensory-motor training; CI = confidence interval; RT = resistance training; VAS = visual analogue scale; TUG = Timed Up and Go test; TINETTI = Tinetti balance assessment tool; MVIC = maximal voluntary isometric contraction; WOMAC = Western Ontario and McMaster Universities osteoarthritis index; *analysis of variance (ANOVA) for repeated measurements; †t test conducted to compare means; T0 = baseline; T16 =16 weeks post-intervention.

frequency (n) and relative frequency (%). The significance level was taken to be 5%.

For the quantitative variables of age, weight, height and body mass index (BMI), the paired Student t test was used, and the results were presented as summary measurements (i.e. the mean). In comparing quantitative variables between the groups, analysis of variance (ANOVA) for repeated measurements was used, and significant differences were taken to exist when $P < 0.05$. In situations in which there was an interaction effect, multiple comparisons were made to identify the differences found. We also estimated Cohen's d effect size index. We classified the Cohen effect sizes as small ($d = 0.2$), medium ($d = 0.5$) or large ($d \geq 0.8$).

There were no changes to the study protocol after the study started. Thus, the study registration protocol was followed exactly as it was written.

RESULTS

Participant flow

Over a six-month period, 120 patients with a diagnosis of knee osteoarthritis were attended at the rheumatology service of the Interlagos specialty clinic. Of these, 96 met the inclusion criteria for this study and were invited to participate in it.

Fifty-six did not meet the inclusion criteria (**Figure 1**). Thus, 64 participants were randomized to SMT or RT, to form two groups of 32 participants each. There was one loss from the follow-up in the sensory motor group because this participant moved to another city and one loss due to low back pain. In the resistance training group, there were no losses from the follow-up. The clinical and demographic characteristics of the participants are shown in **Table 2**.

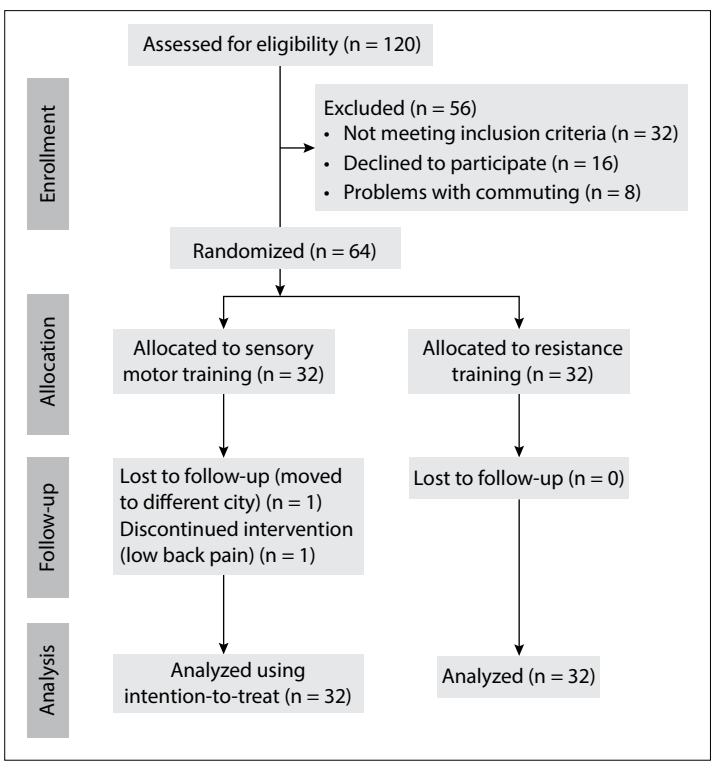


Figure 1. Flow diagram of the progress through the phases of the study.

Pain

The two groups were compared over time (T0 versus T16) and the interaction effect of baseline vs. post-intervention was measured. We observed that at T16, the RT group showed a greater reduction in the outcome of pain: mean difference, MD 0.50; 95% confidence interval, CI -0.66 to 1.66; and $d = 0.24$, i.e. a small effect.

Quality of life

Regarding the SF-36 quality of life questionnaire, we found significant differences between the times evaluated, for the following subscales: physical role functioning, which was better in the RT group (MD 13.1; 95% CI 23.70 to 2.51; $d = 0.14$); vitality, which was better in the RT group (MD 13.9; 95% CI 24.00 to 3.80; $d = 0.25$, i.e. a small effect); emotional role functioning, which was better in the RT group (MD 36.5; 95% CI 55.53 to 17.47; $d = -0.08$); and mental health, which was better in the SMT

Table 2. Participants' characteristics

Variables	Groups				P*
	SMT		RT		
	$\bar{x}$	SD	$\bar{x}$	SD	
Age	61.6	6.8	61.8	6.4	0.895
Height	1.57	0.08	1.59	0.07	0.361
Weight	75.7	13	75.5	12.7	0.949
BMI	24.1	3.8	23.6	3.5	0.587
	n	%	n	%	
Gender					
Male	2	6.3%	1	3.1%	> 0.999
Female	30	93.8%	31	96.9%	
Hypertension†					
Yes	17	53.1%	20	62.5	0.448
No	15	46.9%	12	37.5	
Diabetes† mellitus					
Yes	10	68.8%	4	12.5%	0.070
No	22	31.3%	28	87.5%	
Knee osteoarthritis Kellgren and Lawrence (K&L)					
Grade I	15	46.9%	13	40.6%	0.936
Grade II	9	28.1%	9	28.1%	
Grade III	6	18.8%	7	21.9%	
Grade IV	2	6.3%	3	9.4%	

SMT = sensory-motor training; RT = resistance training; SD = standard deviation; BMI = body mass index. *t test conducted to compare means; chi-square test used to compare proportions. †self-reported by the participants, but diagnosed previously by a physician.

group (MD 8.9; 95% CI 18.11 to 0.31; d = 0.52, i.e. a medium effect). In the SF-36 subscale of physical role functioning, there was an interaction effect between the groups, but there was only a statistically significant difference between the times evaluated for the RT group (P = 0.001). In the subscales of bodily pain, general health perception and social role functioning, we did not find any statistically significant difference between the groups or between the times evaluated. These results are shown in **Table 3**.

Mobility

The two groups were compared at the baseline and after the intervention (T0 versus T16) and the interaction effect was measured. At T16, there were reductions in both groups regarding the outcome of mobility. The reduction was greater in the resistance training group: MD -0.80; 95% CI -1.85 to 0.25; d = -0.67, i.e. a medium effect.

Isometric strength

The two groups were compared at the baseline and after the intervention (T0 versus T16) and the interaction effect was measured. At T16, the SMT group showed greater improvement in the outcome of isometric strength: MD 6.5; 95% CI 0.13 to 12.87; d = 0.55, i.e. a medium effect.

Functional capacity

The two groups were compared at the baseline and after the intervention (T0 versus T16) and the interaction effect was measured. At T16, there were reductions in both groups regarding the outcome of functional capacity, although the reduction was greater in the resistance training group: MD -1.6; 95% CI -6.61 to 9.82; d = 0.09.

Harm

One participant stopped the intervention and withdrew from the study due to low back pain.

DISCUSSION

Summary of main findings

Through searching the literature on this topic, and considering our personal experience, we saw that there was a need to investigate another type of physical exercise for treating osteoarthritis of the knee. In clinical practice, we had observed that not all patients benefited from resistance training, and that this type of exercise might be insufficient to achieve the desired improvements in quality of life and functionality. Thus, the purpose of this study was to compare the effectiveness of two separate types of physical exercise: sensory-motor training versus resistance training, in relation to improvement of pain and functioning within the study population.

In our study, we found significant differences between the groups, in the results relating to VAS, TUG, isometric strength, Tinetti balance scale, WOMAC questionnaire and the SF-36 subscales regarding physical aspects, vitality, emotional aspects and mental health. Thus, we observed improvements in pain, physical function and quality of life in both types of protocols proposed.

Table 3. Scores on the Short Form-36 (SF-36) questionnaire subscales

SF-36		Group				P* (Interaction effect)	P† (Time [T0 versus T16])	Cohen's d
		SMT ($\bar{x}$)	95% CI	RT($\bar{x}$)	95% CI			Effect size post-intervention
Physical role functioning	T0	51.4	43.22-59.58	38.3	31.70-44.90	0.034	0.001	0.14
	T16	54.8	46.26-63.34	51.4	42.57-60.23			
Physical functioning	T0	32.8	19.57-46.03	30.5	16.62-44.38	0.726	< 0.001	0.16
	T16	57.5	42.50-72.50	50.8	37.57-64.03			
Bodily pain	T0	50.4	40.41-60.39	48.0	38.81-57.19	0.886	0.060	0.18
	T16	59.3	50.14-68.46	54.8	45.75-63.85			
General health perceptions	T0	55.8	48.23-63.37	59.8	51.36-68.24	0.425	0.098	-0.06
	T16	60.8	53.88-67.72	62.0	54.57-69.43			
Vitality	T0	55.6	47.99-63.21	46.4	38.72-54.08	0.256	< 0.001	0.25
	T16	64.5	58.41-70.59	60.3	53.13-67.47			
Social role functioning	T0	72.8	62.63-82.97	70.8	59.80-81.80	0.465	0.932	0.29
	T16	74.0	65.78-82.22	67.3	57.89-76.71			
Emotional role functioning	T0	34.7	19.38-50.02	28.1	14.76-41.44	0.261	< 0.001	-0.08
	T16	61.1	46.25-75.96	64.6	49.96-79.24			
Mental health	T0	65.2	57.63-72.77	60.5	52.86-68.14	0.399	0.006	0.52
	T16	74.1	68.22-79.98	65.6	58.75-72.45			

SMT = sensory-motor training; CI = confidence interval; RT = resistance training. *Analysis of variance (ANOVA) for repeated measurements; †paired t test conducted to compare means. T0 = baseline; T16 = 16 weeks post-intervention.

However, through estimating the Cohen's d effect size, we observe that there were small effects towards the SMT group regarding pain measured using the VAS (d = 0.24) and regarding the SF-36 subscales of vitality (d = 0.25) and social role functioning (d = 0.29). There were medium effects regarding mental health (d = 0.52) and maximal voluntary isometric contraction (MVIC) (d = 0.55).

Regarding the effect size for resistance training, there was a medium effect on mobility (d = -0.67) and a small effect on balance (d = -0.22).

Comparison with similar studies

We found only one other study[15] that evaluated sensory-motor (proprioceptive) training among patients with knee osteoarthritis, and the findings from that study were similar to our results relating to pain. That study consisted of randomized controlled trial on 22 patients with bilateral knee osteoarthritis, in which a proprioceptive training program (n = 12) was compared with a control group (n = 10). The training group performed 11 different proprioceptive exercises for balance and coordination, twice a week for six weeks. This group that underwent sensory-motor training presented a significant reduction in perceived pain (as measured using a VAS) during activities of daily life and in performing functional tests after the physical exercise program ($P < 0.05$).

Using WOMAC, we observed that the effect size was insignificant. This agreed with the findings regarding pain and function from two studies[12,19] in which sensory-motor training was performed in association with muscle-strengthening training, among patients with knee osteoarthritis. Diracoglu et al.[19] compared the effectiveness of exercises for balance and kinesthesia training together with strengthening exercises versus strengthening exercises alone, among 60 participants. The patients received 24 training sessions over a period of eight weeks, and although the results indicated that both groups improved, there was no difference in the WOMAC questionnaire between the groups. The results from the SF-36 subscales of functional capacity, physical aspects and vitality and from the 10-minute walk test in the group that underwent balance and kinesthesia training were also better.[19] Fitzgerald et al.[12] compared a group of knee osteoarthritis patients who underwent a traditional training program (muscle strengthening of the lower limbs associated with stretching and joint amplitude gain exercises) with a group that performed the traditional program plus sensory training (agility and coordination). In both studies,[12,19] although the groups that had additional sensory-motor training achieved improvements, the authors did not find any significant difference in comparison with the traditional rehabilitation program.

In our study, the isometric quadriceps strength improved in both groups. Although a medium effect size was observed in the SMT group, the values were not significantly different from those of the RT group after training. There were no changes in isokinetic strength in either group after the intervention period. We suggest that use of a proprioceptive exercise program may improve postural control and functional capacity, while decreasing perceived knee pain among patients with bilateral knee osteoarthritis.[12,19,20]

Implication for further research and practice

Although it was hard to establish a comparison between our study and those cited above because of methodological differences, the results from our study suggest that sensory-motor training may be a plausible alternative, with a small effect towards this training in relation to pain and a medium effect in relation to MVIC. RT showed a small effect on balance and a medium effect on mobility. Regarding professional practice, we can hypothesize that the two types of exercises together can complement each other.

Limitation of the study

One limitation of our study was the number of participants. In calculating the sample size, we reached a number that we were unable to recruit. Thus, the power of the study was reduced.

CONCLUSION

Both resistance training for the lower limbs and sensory-motor training led to reduction of perceived pain and increased mobility in the study population. There were also improvements in functional capacity and isometric strength. The negative impact of knee osteoarthritis on the quality of life was attenuated through practicing any of the types of physical exercise training.

Based on our findings, resistance training and sensory-motor training for the lower limbs among patients with knee osteoarthritis seemed to present similar effects on pain and function. However, because there was a considerable risk of type 2 error, further randomized clinical trials are still needed to provide a sound conclusion.

REFERENCES

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377(9783):2115-26.
2. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage. 2011;19(5):478-82.
3. Walsh NE, Pearson J, Healey EL. Physiotherapy management of lower limb osteoarthritis. Br Med Bull. 2017:122(1):151-61.
4. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-88.
5. Bartholdy C, Juhl C, Christensen R, et al. The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and

meta-regression analysis of randomized trials. Semin Arthritis Rheum. 2017;47(1):9-21.
6. Bennell KL, Dobson F, Hinman RS. Exercise in osteoarthritis: moving from prescription to adherence. Best Pract Res Clin Rheumatol. 2014;28(1):93-117.
7. Loew L, Brosseau L, Kenny GP, et al. An evidence-based walking program among older people with knee osteoarthritis: the PEP (participant exercise preference) pilot randomized controlled trial. Clin Rheumatol. 2017;36(7):1607-16.
8. Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. J Sci Med Sport. 2011;14(1):4-9.
9. O'Reilly SC, Jones A, Muir KR, Doherty M. Quadriceps weakness in knee osteoarthritis: the effect on pain and disability. Ann Rheum Dis. 1998;57(10):588-94.
10. Rogers MW, Tamulevicius N, Coetsee MF, Curry BF, Semple SJ. Knee Osteoarthritis and the Efficacy of Kinesthesia, Balance & Agility Exercise Training: A Pilot Study. Int J Exerc Sci. 2011;4(2):124-32.
11. Scopaz KA, Piva SR, Gil AB, et al. Effect of baseline quadriceps activation on changes in quadriceps strength after exercise therapy in subjects with knee osteoarthritis. Arthritis Rheum. 2009;61(7):951-7.
12. Fitzgerald GK, Piva SR, Gil AB, et al. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Phys Ther. 2011;91(4):452-69.
13. Fitzgerald GK, Piva SR, Irrgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. Arthritis Rheum. 2004;51(6):941-6.
14. Fitzgerald GK, Piva SR, Irrgang JJ, Bouzubar F, Starz TW. Quadriceps activation failure as a moderator of the relationship between quadriceps strength and physical function in individuals with knee osteoarthritis. Arthritis Rheum. 2004;51(1):40-8.
15. Sekir U, Gür H. A multi-station proprioceptive exercise program in patients with bilateral knee osteoarthrosis: functional capacity, pain and sensoriomotor function. A randomized controlled trial. J Sports Sci Med. 2005;4(4):590-603.
16. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. Arthritis Rheum. 1995;38(11):1541-6
17. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36) [Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure]. Rev Bras Reumatol. 1999; 39(3):143-50.
18. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. Phys Ther. 1997;77(8):812-9.
19. Diracoglu D, Aydin R, Baskent A, Celik A. Effects of kinesthesia and balance exercises in knee osteoarthritis. J Clin Rheumatol. 2005;11(6):303-10.
20. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev. 2015;1:CD004376.

This study was presented as a master's thesis to the Universidade Federal de São Paulo (UNIFESP) in 2012 and was registered at ClinicalTrials under protocol number NCT01529398

Sources of funding: The study did not have any financial support

Conflict of interest: The authors declare that they did not have any conflict of interest

Date of first submission: June 5, 2017

Last received: August 24, 2017

Accepted: September 10, 2017

Address for correspondence:
Antonio Jose Grande
Av. Dom Antônio Barbosa, 4.155
Vila Santo Amaro — Campo Grande (MS) — Brasil
CEP 79115-898
Cel. (+55 67) 99959-9877
E-mail: grandeto@gmail.com

Educational inequality in Rio de Janeiro and its impact on multimorbidity: evidence from the Pró-Saúde study. A cross-sectional analysis

Adelson Guaraci Jantsch[I], Ronaldo Fernandes Santos Alves[II], Eduardo Faerstein[III]

Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Rio de Janeiro (RJ), Brazil

[I]MD, MSc. Doctoral Student, Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro (UERJ), and Coordinator, Residency Program in Family and Community Medicine, Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro (RJ), Brazil.

[II]MSc. Doctoral Student, Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro (RJ), Brazil.
orcid.org/0000-0002-8358-0519

[III]MSc, PhD. Associate Professor, Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Rio de Janeiro (RJ), Brazil.

KEY WORDS:
Comorbidity.
Health status disparities.
Educational status.
Cross-sectional studies.

ABSTRACT

BACKGROUND: Information about multimorbidity is scarce in developing countries. This study aimed to estimate the association of educational attainment with occurrences of multimorbidity in a population of public employees on university campuses in Rio de Janeiro.

DESIGN AND SETTING: We conducted cross-sectional analyses on baseline data (1999-2001) from 3,253 participants in the Pró-Saúde study, conducted in Brazil.

METHODS: The prevalence of multimorbidity, defined as a self-reported history of medical diagnoses of two or more chronic conditions, was estimated according to sex, age, smoking, obesity and educational level. The association between education and multimorbidity was estimated using odds ratios (OR) and the relative and slope indices of inequality, in order to quantify the degree of educational inequality among individuals with multimorbidity in this population.

RESULTS: Greater age, female sex, smoking and obesity had direct associations with multimorbidity; and tobacco exposure and obesity also showed direct relationships with poorer educational level. There was a monotonic inverse linear trend between educational level and the presence of multimorbidity among women, with twice the odds (OR 2.47; 95% confidence interval, CI: 1.42-4.40) between extremities of schooling categories. There was excess multimorbidity of 22% at the lowest extremity of schooling, thus showing that women with worse educational status were more affected by the outcome. No trend and no excess multimorbidity was seen among men.

CONCLUSIONS: Educational inequality is an important determinant for development of multimorbidity. Men and women experience its effect differently. Researchers need to consider that sex may be an effect modifier in multimorbidity studies.

INTRODUCTION

Multimorbidity, defined as the coexistence of two or more chronic conditions in the same patient,[1-3] has been consistently correlated with several outcomes, such as greater use of healthcare services,[3] poor quality of life,[4] polypharmacy and adverse drug events,[5] functional decline,[6] disability,[7] hospitalization[8] and higher risk of death.[9] This concept changes the way of looking at co-occurrence of multiple diseases in a single person. Traditionally, the approach taken in cases of patients with multiple conditions has been that they have one protagonist disease that is influenced by a group of concurrent conditions (comorbidities). In multimorbidity, there are no main diseases. All of them have their own importance within the patient's clinical picture.

Most studies on multimorbidity have been conducted in high-income countries (HIC) in Europe, North America and Australia, where it affects the majority of the population older than 65 years.[10] Like in many single diseases and risk factors, age is the main determinant for its occurrence. Moreover, studies have shown that multimorbidity is a major topic of concern relating to health inequalities[11,12] because of its association with low socioeconomic position, measured via household income[13] or educational attainment.[14] Proximal determinants, such as obesity,[15] smoking, alcohol consumption and lack of physical activity have also been identified.[16]

Evidence is scarce regarding its determinants and impact in low and middle-income countries (LMIC), where population dynamics, social development, epidemiological patterns and healthcare services may differ from those in HIC.[17,18] Some studies in LMIC have also shown an

association between low socioeconomic position and multimorbidity,[19-21] but the determinants of multimorbidity are still insufficiently studied in LMIC.[22,23]

The few studies conducted in Brazil were restricted to specific populations. They showed that multimorbidity was associated with higher risk of death and readmission after hospital discharge, among elderly people.[24] It was also associated with aging and obesity and with worse self-perception of health among women;[25,26] and it was highly prevalent among elderly people using public primary healthcare services.[27]

In addition, several methodological issues relating to studies on multimorbidity are still unresolved.[1,28] These include what the best way to measure it would be,[29] which clusters of diseases are more harmful[30] and what role sex has in relation to development of multimorbidity.[31]

The aims of the present study were to determine the prevalence of multimorbidity in a population of adult Brazilians and to investigate the relationship between its occurrence and socioeconomic position, measured via educational attainment.

METHODS

Study design

Our study was a cross sectional analysis that was carried out using data from the baseline of the Pró-Saúde study (PSS). PSS is a longitudinal investigation program on public employees on university campuses in Rio de Janeiro, Brazil, who were not members of the teaching staff. It has mainly focused on social determinants of health.[32]

This study was approved by the Research Ethics Committee of Pedro Ernesto University Hospital (record 224/1999 and record 461/2001).

Data collection

Between 1999 and 2012, four phases of data collection were conducted, including self-completion of questionnaires, anthropometric measurements and other tests. The PSS baseline was composed of 3,253 subjects who formed part of the inventory both in phase 1 (1999) and in phase 2 (2001-2).

Pregnant women and people over 69 years of age were considered ineligible for this study. These exclusions left the sample with 3,251 individuals.

PSS data were collected using a multidimensional, self-completed questionnaire administered in the workplace. A pilot study and test-retest reliability studies, and independent double data entry, were performed to ensure data quality.[33]

Outcome

Self-reported information about chronic medical conditions was obtained both from the 1999 and from the 2001 data collection phases through the following question: "Have you ever been informed by any physician that you had...?". This question was applied to a list of 14 different clinical conditions: hypertension, diabetes, dyslipidemia, angina, ischemic heart disease, stroke, asthma, chronic obstructive pulmonary disease, cholecystitis, peptic ulcer, repetitive strain injury, osteoarthritis, hyperthyroidism and hypothyroidism. Each condition only had two response options (yes/no). Hypertension, diabetes, dyslipidemia, stroke, cholecystitis, peptic ulcer, repetitive strain injury and osteoarthritis were considered to be single diseases. Angina and ischemic heart disease were aggregated into one condition, labeled as "coronary heart disease". Asthma and chronic obstructive pulmonary disease were aggregated as "lung condition". Hyperthyroidism and hypothyroidism were aggregated as "thyroid condition". The dependent variable of multimorbidity was defined as a self-reported medical diagnosis of two or more of these 11 chronic conditions in the same person.[2]

Study variables

Our main exposure of interest was education attainment, as a marker of individual socioeconomic status. Data were collected in 1999 in seven different categorical levels: incomplete elementary school, completed elementary school, incomplete high school, completed high school, incomplete university, completed university and postgraduate studies. Sex, smoking status, obesity and age were studied as intervenients of the process, and these data were collected in 2001. The respondent was considered to have been exposed to tobacco if he/she answered "yes, I am exposed to tobacco" or "I used to be, in the past, but not anymore". The option "never have been" was considered to represent non-exposure. Obesity was evaluated by means of a double measurement of abdominal circumference at the level of the navel and was defined according to abdominal circumference thresholds of 88 cm for women and 102 cm for men, as suggested by the World Health Organization (WHO).[34] Age was used as a discrete variable, in years.

Statistical analysis

Frequencies of multimorbidity, smoking status and obesity were calculated according to sex and for each educational level. Prevalences and 95% confidence intervals were calculated using the chi-square test for linear trend, regarding educational levels and multimorbidity. We performed these analyses for the whole population and stratified according to sex.

Age-adjusted logistic regression models were built to examine predictors of multimorbidity (model 1). We then explored the mediating effects of smoking status and obesity in the age-adjusted models (model 2). Adjusted odds ratios and 95% confidence intervals for multimorbidity on each educational level were calculated for both models.

Finally, we estimated the degree of educational inequality in occurrences of multimorbidity by calculating the slope index of inequality (SII) and relative index of inequality (RII). These indices have the capacity to produce absolute and relative estimates of the socioeconomic gradient relating to health, and they are based on weighted linear and logistic regression analysis, respectively.[35,36]

For this calculation, the exposure was transformed from an ordinal categorical variable into a continuous variable, composed of a series of numerical values between 0 and 1 that represented the median of the cumulative interval in each category. Each new value was used in the related regression models according to the numerical score, which represented the proportional size of the population in each category, taking into account the information from all simultaneous levels and the relative positions of the value within the population scale.

In this manner, SII and RII provide measurements of the relationship between socioeconomic status and the health outcome that are more reliable. Since 2013, the World Health Organization has recommended that SII and RII should be used as indicators for reporting on health inequalities. These indices make the notions of excess and relative risk between two hypothetical extremities more reliable and comprehensible than do the traditional measurements (odds ratios, OR, and relative risk, RR), through log-linear and linear models, respectively.[36,37]

All analysis were performed using the R statistical package (version 3.3.1) and P-values < 0.05 were defined as statistically significant.

RESULTS

All of the 3,251 subjects at the baseline answered the questions about their educational level and filled out the morbidity inventory. 107 subjects did not provide information about their tobacco status and 52 did not have their abdominal circumferences measured, thus totaling 159 subjects with missing data. There were no differences between these 159 subjects and the other 3,092 regarding educational attainment and the prevalence of multimorbidity. Therefore, we considered this to be a situation of random missing data. Hence, the analytical sample comprised 3,092 subjects aged between 24 and 69 years. There were 1,378 men (44.6%) and 1,714 women (55.4%), with average ages of 41.3 years (95% confidence interval, CI 40.9-41.8) and 42.5 years (95% CI: 42.2-42.9), respectively.

The women had higher educational levels than the men and for both sexes, people with high levels of education tended to be younger. The women had a lower rate of tobacco use, such that 39.8% of them had used it during their lifetime, versus 45.1% of the men. However, obesity was more common among the women (43.6%) than among the men (24.2%). The prevalence of multimorbidity was 27.3% among the men and 37.8% among the women. These data are summarized in **Table 1**.

The associations between educational level and presence of chronic conditions according to sex are shown in **Table 2**. Hypertension, dyslipidemia, repetitive strain injury and osteomuscular problems were the most common chronic conditions reported by both men and women. Every condition analyzed in this study, except repetitive strain injury, showed a significant linear trend among the women, such that these conditions were always more prevalent among those with low educational levels. The men showed a less pronounced trend among educational levels, which was statistically significant only for hypertension, diabetes, coronary heart disease, repetitive strain injury and peptic ulcer. Stroke and thyroid disease did not present any trend among the men and very low prevalence as well. Subjects in the highest education categories were less exposed to tobacco over the courses of their lives, with the same linear trend for both sexes. The same educational gradient was observed in relation to obesity among the women, but not among the men.

The association between educational level and multimorbidity differed between the men and women and can be seen in **Table 3**. The women showed a linear gradient across the educational levels, such that those with incomplete elementary school presented more than twice the chance of occurrences of multimorbidity in relation to those who had done postgraduate studies (OR = 2.77; 95% CI: 1.61-4.91). On the other hand, the men did not show any gradient in the age-adjusted model, such that there was a lower chance of multimorbidity among those with incomplete and complete elementary school, but this was not statistically significant.

Table 1. Descriptive analysis on the Pró-Saúde study baseline (1999-2001), Rio de Janeiro

	General		Men		Women	
	N	%	N	%	N	%
	3,092	100	1,378	44.6	1,714	55.4
Age						
Mean	42.00 (41.70-42.30)		41.33 (40.9-41.8)		42.55 (42.2-42.9)	
Minimum-maximum	24-69		24-68		25-69	
Education						
Postgraduate	515	16.7	170	12.3	345	20.1
Complete university	803	26.0	325	23.6	478	27.9
Incomplete university	433	14.0	204	14.8	229	13.4
Complete high school	659	21.3	306	22.2	353	20.6
Incomplete high school	274	8.9	145	10.5	129	7.5
Complete elementary	178	5.8	96	7.0	82	4.8
Incomplete elementary	230	7.4	132	9.6	98	5.7
Tobacco exposure						
Smoker	675	21.8	335	24.3	340	19.8
Former smoker	629	20.3	286	20.8	343	20.0
Never smoker	1,788	57.8	757	54.9	1,031	60.2
Obesity						
Obese	1,082	35.0	334	24.2	748	43.6
Non-obese	2,010	65.0	1,044	75.8	966	56.4

Since obesity and smoking were influenced by socioeconomic position and had an impact on the occurrence of the outcome, they were considered, along with age, to be potentially intervening factors in the relationship between education and multimorbidity. However, their presence in the age-adjusted models only slightly decreased the association between low educational level and occurrences of multimorbidity among the women. Among the men, the same pattern of no tendency across the social gradient was observed. Although the women had higher prevalence of obesity and a marked gradient across all educational levels, the point estimate of its effect on occurrences of multimorbidity was greater among the men (for men, OR = 2.19; 95% CI: 1.65-2.90; versus for women, OR = 1.90; 95% CI: 1.51-2.39). The opposite association was seen in relation to tobacco exposure, such that the men presented higher prevalence, but the association with multimorbidity was statistically significant only among the women (for men, OR = 1.27; 95% CI: 1.01-1.59; versus for women, OR = 1.20; 95% CI: 0.91-1.59).

SII and RII were then calculated using the same models. For the women, the excess multimorbidity at the lowest educational level was 22%, in comparison with the highest level (SII = 22.03; 95% CI: 14.2-29.8). In relative terms, there was a three times greater chance of presenting multimorbidity at the lowest extremity in relation to the highest educational level (RII = 2.97; 95% CI: 1.94-4.54), thus showing that there was a high level of inequality among the women in this population. For the men, after adjustment for age, smoking status and obesity, there was no statistical difference in either index across the population (RII = 0.74; 95% CI: 0.45-1.23; and SII = -3.4; 95% CI: -11.6-4.8).

Table 2. Prevalence of morbidities, tobacco exposure, obesity and multimorbidity according to educational level at the Pró-Saúde study (PSS) baseline (1999-2001), Rio de Janeiro (RJ), Brazil

	Total	Educational level							P-value
		Postgraduate studies	Complete university	Incomplete University	Complete high school	Incomplete high school	Complete elementary	Incomplete elementary	
Men									
Hypertension	28.2	27.6	17.2	28.4	30.7	37.9	31.2	36.4	< 0.001
Diabetes	5.5	4.7	1.5	2.9	6.5	9.7	9.4	10.6	< 0.001
Dyslipidemia	22.0	25.9	18.1	19.6	21.9	28.3	21.9	23.5	0.37
Coronary heart disease	2.4	1.8	0.9	1.0	2.0	2.1	8.3	6.1	< 0.001
Stroke	0.6	1.2	0.6	0.0	0.3	0.0	3.1	0.0	0.95
Lung condition	2.1	2.3	2.5	2.4	2.0	2.1	2.1	0.8	0.31
Peptic ulcer	5.3	2.3	3.1	4.4	4.9	9.7	11.5	7.6	< 0.001
Cholecystitis	2.2	3.5	1.5	2.0	1.3	2.8	4.2	2.3	0.78
Repetitive strain injury	10.3	12.3	12.6	11.3	9.5	10.3	4.2	6.8	< 0.001
Osteomuscular	7.8	8.2	5.2	4.4	9.1	11.0	8.3	12.1	0.01
Thyroid disease	0.4	0.0	0.6	0.5	0.3	0.7	1.0	0.0	0.86
Tobacco exposure	45.1	37.6	30.5	34.8	48.0	60.0	70.8	64.4	< 0.001
Obesity	24.2	27.1	18.5	27.9	26.1	24.8	22.9	25.0	0.55
Multimorbidity	23.7	22.9	17.5	22.1	23.8	33.1	27.1	28.8	0.002
Women									
Hypertension	30.6	14.8	18.4	30.1	36.0	48.1	67.1	74.5	< 0.001
Diabetes	4.9	1.7	2.5	3.5	5.1	10.1	15.8	14.3	< 0.001
Dyslipidemia	24.0	19.1	21.1	24.9	21.8	31.0	30.5	46.9	< 0.001
Coronary heart disease	2.6	1.4	1.3	0.4	2.5	70.	6.1	10.2	< 0.001
Stroke	0.7	0.3	0.2	0.4	0.8	2.3	2.4	1.0	0.009
Lung condition	4.7	2.9	3.6	5.7	4.2	10.8	4.9	8.2	0.002
Peptic ulcer	5.5	3.2	4.6	3.9	6.5	9.3	12.2	8.2	< 0.001
Cholecystitis	6.2	5.2	4.6	5.2	6.5	5.4	15.8	12.2	< 0.001
Repetitive strain injury	23.6	22.3	19.2	32.3	25.2	23.3	20.7	25.5	0.25
Osteomuscular	1.6.0	7.2	8.6	14.8	19.3	22.5	39.0	46.9	< 0.001
Thyroid disease	4.9	6.1	6.3	3.1	3.1	7.0	3.7	3.1	0.08
Tobacco exposure	39.8	33.9	35.6	38.9	41.6	59.7	45.1	46.9	< 0.001
Obesity	43.6	32.8	34.1	41.9	51.0	54.3	67.1	72.4	< 0.001
Multimorbidity	34.2	22.6	21.7	33.6	37.7	51.9	68.3	72.4	< 0.001
Whole population									
Multimorbidity	29.5	22.7	20.0	28.2	31.2	42.0	46.1	47.4	< 0.001*

*P-value for linear trend.

DISCUSSION

To the best of our knowledge, this was the first study to describe the impact of educational inequality on multimorbidity in an adult population in Brazil. Despite difficulties that have been mentioned in systematic reviews regarding comparisons of the prevalences of multimorbidity in different countries,[7,38] the prevalence of multimorbidity of 33.1% that we observed in our study was close to the prevalences found in developed countries such as the Netherlands,[39] Canada[13] and Australia,[40] but it was considerably higher than in other LMIC countries.[19-21]

As expected, the prevalence of multimorbidity increased with age and was higher among women than among men, across educational levels. Both obesity and smoking status showed high prevalence in the study population and these had significant relationships with the outcome, albeit in different ways. The men tended to be more exposed to tobacco over the course of their lives, but the effect of tobacco exposure on multimorbidity was perceived especially among the women. On the other hand, the women tended to be more obese, with a clear social gradient, but the effect of obesity on multimorbidity was stronger among the men. This kind of information is very important for understanding the paths that are followed until occurrences of multimorbidity are observed.

Hypertension, dyslipidemia, repetitive strain injury and osteomuscular problems were the most prevalent chronic conditions reported both by men and women. However, regarding the distribution of these problems across the different socioeconomic statuses, the women showed marked trends towards high prevalence of almost every chronic condition, among those at the lowest educational level, except in relation to repetitive strain injury and thyroid diseases. Among the men, this trend was only noticeable in relation to hypertension, diabetes, coronary heart disease and peptic ulcer, but not with the same intensity as seen among the women. Stroke showed very low prevalence in this study, thus making it impossible to infer any tendency across the population.

The association between educational level and multimorbidity differed substantially regarding sex in the multivariate adjusted models. Among the women, there was a monotonic and inverse linear trend between educational level and occurrences of multimorbidity, with a threefold greater chance (RII = 2.97; 95% CI: 1.94-4.54) of the outcome between the extremities of schooling. The SII revealed that there was excess prevalence of multimorbidity of 22% among the women at the lowest educational level.

Education is a lifelong process and a lack of opportunities for receiving education represents a considerable disadvantage for children's health.[41] People who are less educated and/or spent their childhoods living in poor socioeconomic conditions have worse health outcomes than do people who had access to education, enjoyed good housing conditions and did not experienced food insecurity during the first years of their lives. The major concern of the WHO Commission on Social Determinants of Health[42] is that developing countries have a considerable educational gap between rich and poor people, and an even larger gap between men and women.

Our results agree with those observed in several other studies, in which educational inequality played an important role in the development of multimorbidity.[20,43-45] But the remarkable fact in the present study is that this trend was detected only among women. Among men, no trend across the social gradient was observed (RII 0.74; 95% CI: 0.45-1.23; and SII = -3.4; 95% CI: -11.6-4.8).

Table 3. Age and multivariate adjusted odds ratio (OR, 95% confidence interval [CI]) and slope index of inequality and relative index of inequality for multimorbidity according to educational level among men and women at the Pró-Saúde study baseline (1999-2001), Rio de Janeiro (RJ), Brazil

	Women		Men	
	Age-adjusted	Multivariate adjusted OR (95% CI)	Age-adjusted	Multivariate adjusted OR (95% CI)
Obesity		1.90* (1.51-2.39)		2.19* (1.65-2.90)
Tobacco		1.27* (1.01-1.59)		1.20 (0.91-1.59)
Education				
Postgraduate studies	1	1	1	1
Complete university	0.85 (0.60-1.0)	0.83 (0.59-1.19)	0.84 (0.53-1.37)	0.90 (0.56-1.47)
Incomplete university	1.92† (1.29-2.85)	1.79* (1.21-2.68)	1.15 (0.69-1.91)	1.11 (0.66-1.86)
Complete high school	1.43‡ (1.01-2.05)	1.33 (0.92-1.90)	0.90 (0.57-1.44)	0.91 (0.57-1.46)
Incomplete high school	2.05† (1.30-3.24)	1.85† (1.16-2.94)	1.24 (0.74-2.09)	1.26 (0.74-2.15)
Complete elementary	3.6* (1.74-5.46)	2.75* (1.56-4.92)	0.66 (0.36-1.21)	0.69 (0.37-1.28)
Incomplete elementary	2.77* (1.61-4.91)	2.47* (1.42-4.40)	0.68 (0.39-1.19)	0.70 (0.40-1.24)
Slope index of inequality		22.03* (14.2-29.8)		-3.4 (-11.6-4.8)
Relative index of inequality		2.97* (1.94-4.54)		0.74 (0.45-1.23)

P-value: * ≤ 0.001; † ≤ 0.01; ‡ ≤ 0.05.

It was beyond the scope of the present study to explore the singularities of the prevalence, determinants and burden of multimorbidity relating to differences between the sexes. Nonetheless, the findings showed different effects on the outcome from exposures and intervenients, which raises some important questions about this subject, especially relating to the way in which measurements are made.

We could easily infer from our data that educational inequality is unrelated to occurrences of multimorbidity in the male population. However, recent evidence in the literature[14,20,44] shows that this statement lacks plausibility. This makes us look at this issue from another angle, which is: why did the women in this study show a monotonic and inverse linear trend between educational level and the presence of multimorbidity, but the men did not?

The prevalence of multimorbidity is absolutely intertwined with the way in which it is measured. Differences within[38] and between similar countries[28] can sometimes be of considerable magnitude in different studies. One possible explanation for this sex-related pattern concerns the historical time at which the data were collected. Between 1999 and 2001, i.e. the period during which the PSS baseline data were collected, the city of Rio de Janeiro already had a very extensive hospital network, albeit disorganized and disjointed with the fledgling system of primary healthcare. At that time, the Family Health Strategy (Brazilian federal policy for primary healthcare) coverage in the municipality was only 3%, which was the lowest among Brazilian state capitals.[46] If access is the first attribute of primary healthcare,[47] knowing the way in which these individuals accessed and used the reference healthcare services (if they had any) may be crucial for interpreting our findings.

Contact with a healthcare service is essential for a diagnosis to be made. The way in which morbidities are commonly measured, i.e. by asking "Have you ever been informed by any physician that you had...?", makes it impossible for a person with no access to health services to answer this question. This would not be a matter of such concern if equity between the sexes regarding access to healthcare services existed, but this was not the case in Brazil in 2001[48] and it is not the case in many LMIC,[42,49] where specific health interventions like cervical cancer screening, prenatal care, contraception and child care may provide selective access for women, but not for men. Thus, women are more exposed to healthcare providers and they are therefore more likely to be diagnosed with a chronic condition. For example, the prevalence of multimorbidity was found to be only 4% among South African adults and 70% of them were women.[19]

For this reason, considering that the construct of multimorbidity measures not only the current health status of a population but also the health inequalities inherent to the healthcare system, it is crucial to understand the complexity of this phenomenon. Moreover, beyond these absolute inequalities, there is a relative difference among people relating to the way in which they interact with healthcare services, and this relates both to healthcare professionals and to patients. From this angle, the concept of "multimorbidity", which is thought to be a good way to capture the current status of chronic conditions in a population, ends up also capturing the relationship between individuals and the healthcare services.

In addition to the inequalities in healthcare access that lead to differences in the prevalences of chronic conditions and multimorbidity between men and women, it may be also possible that these outcomes could have a closer relationship with women than with men. There is some evidence suggesting that people tend to develop different morbidity patterns, depending on their sex.[31] Women might be more prone to develop chronic conditions that lead them to frailty and functional disability, while men could tend to develop chronic conditions that shorten their lives, i.e. leading them to premature death. If this is the case, different diseases would form the conditions of multimorbidity observed for each sex, but there would not be any differences in prevalence. This subject was not the focus of our study but, even if this phenomenon were to occur in this population, it would not explain why we did not see the same gradient of multimorbidity among men and women across educational levels.

Gender needs to be studied at least as an effect modifier, because of its different relationship with the outcome and the underlying way in which it is measured. The same reasoning applies to describing the healthcare system within which studies on multimorbidity are conducted. If there is a difference in the accessibility of healthcare services between men and women in a population, thereby representing an absolute inequality in health, the data analysis needs to be stratified according to sex. With unequal access to healthcare services, inferences about multimorbidity cannot be made in the same way that is done in studies conducted in high-income and countries and in those with strong primary healthcare. Nonetheless, we can use such inferences to take a better look at healthcare services and socioeconomic inequalities.

CONCLUSION

The evidence gathered here is consistent with what is available in the literature, and it shows that educational inequality is an important determinant for the development of multimorbidity. However, contrary to findings from studies conducted in wealthier countries, men and women experienced this association differently, thus highlighting that gender needs to be taken into consideration as a potential effect modifier in future studies on multimorbidity.

REFERENCES

1. Valderas JM, Mercer SW, Fortin M. Research on patients with multiple health conditions: different constructs, different views, one voice. Journal of Comorbidity. 2011;1:1-3. Available from: www.jcomorbidity.com/index.php/test/article/download/11/15. Accessed in 2017 (Oct 5).
2. Valderas JM, Sibbald B, Salisbury C, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009;(7):357-63.
3. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. BMC Fam Pract. 2014;15:61.
4. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes. 2004;2:51.
5. Calderón-Larrañaga A, Poblador-Plou B, González-Rubio F, et al. Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? Br J Gen Pract. 2012;62(605):e821-6.
6. Marengoni A, von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. J Intern Med. 2009;265(2):288-95.
7. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2013;35:75-83.
8. France EF, Wyke S, Gunn JM, et al. Multimorbidity in primary care: a systematic review of prospective cohort studies. Br J Gen Pract. 2012;62(597):e297-307.
9. Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr. 2016;67:130-8.
10. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. JAMA. 2012;307(23):2493-4.
11. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.
12. Orueta JF, Nuño-Solinís R, García-Alvarez A, Alonso-Morán E. Prevalence of multimorbidity according to the deprivation level among the elderly in the Basque Country. BMC Public Health. 2013;13:918.
13. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. 2015;35(6):87-94.
14. Nagel G, Peter R, Braig S, et al. The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort. BMC Public Health. 2008;8:384.
15. Booth HP, Prevost AT, Gulliford MC. Impact of body mass index on prevalence of multimorbidity in primary care: cohort study. Fam Pract. 2014;31(1):38-43.
16. Fortin M, Haggerty J, Almirall J, et al. Lifestyle factors and multimorbidity: a cross sectional study. BMC Public Health. 2014;14:686.
17. Frenk J, Frejka T, Bobadilla J, et al. La transición epidemiológica en América Latina. Bol Of Sanit Panam. 1991;111(6):485-96.
18. Duarte EC, Barreto SM. Transição demográfica e epidemiológica: a Epidemiologia e Serviços de Saúde revisita e atualiza o tema. Epidemiol Serv Saúde. 2012;21(4):529-32.
19. Alaba O, Chola L. The social determinants of multimorbidity in South Africa. Int J Equity Health. 2013;12:63.
20. Chung RY, Mercer S, Lai FT, et al. Socioeconomic Determinants of Multimorbidity: A Population-Based Household Survey of Hong Kong Chinese. PLoS One. 2015;10(10):e0140040.
21. Ha NT, Le NH, Khanal V, Moorin R. Multimorbidity and its social determinants among older people in southern provinces, Vietnam. Int J Equity Health. 2015;14:50.
22. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. Milbank Q. 2005;83(4):731-57.
23. Afshar S, Roderick PJ, Kowal P, Dimitrov BD, Hill AG. Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys. BMC Public Health. 2015;15:776.
24. Sousa-Muñoz RL, Ronconi DE, Dantas GC, Lucena DMS, Silva IBA. Impacto de multimorbidade sobre mortalidade em idosos: estudo de coorte pós-hospitalização [Impact of multimorbidity on mortality in elderly: a post-hospitalization cohort study]. Rev Bras Geriatr Gerontol. 2013;16(3):579-89.
25. de S Santos Machado V, Valadares AL, Costa-Paiva LH, et al. Aging, obesity, and multimorbidity in women 50 years or older: a population-based study. Menopause. 2013;20(8):818-24.
26. de Souza Santos Machado V, Valadares AL, da Costa-Paiva LS, Moraes SS, Pinto-Neto AM. Multimorbidity and associated factors in Brazilian women aged 40 to 65 years: a population-based study. Menopause. 2012;19(5):569-75.
27. Nunes BP, Thumé E, Facchini LA. Multimorbidity in older adults: magnitude and challenges for the Brazilian health system. BMC Public Health. 2015;15(1):1172.
28. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. J Gerontol A Biol Sci Med Sci. 2011;66(3):301-11.
29. Diederichs CP, Wellmann J, Bartels DB, et al. How to weight chronic diseases in multimorbidity indices? Development of a new method on the basis of individual data from five population-based studies. J Clin Epidemiol. 2012;65(6):679-85.
30. van den Bussche H, Koller D, Kolonko T, et al. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health. 2011;11:101.
31. Verbrugge LM. Gender and health: an update on hypotheses and evidence. J Health Soc Behav. 1985;26(3):156-82.
32. Faerstein E, Chor D, Lopes CS, Werneck GL. Estudo Pró-Saúde: características gerais e aspectos metodológicos [The Pro-Saude Study: general characteristics and methodological aspects]. Rev Bras Epidemiol. 2005;8(4):454-66.

33. Chor D, Faerstein E, Alves MG, de Souza Lopes C. How reproducible is self-reported information on exposure to smoking, drinking, and dietary patterns? Evidence among Brazilian adults in the Pró-Saúde Study. Sao Paulo Med J. 2003;121(2):63-6.
34. World Health Organization. Waist Circumference and Waist-Hip Ratio. Report of a WHO Expert Consultation. Geneva: World Health Oorganization; 2008. Available from: http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf. Accessed in 2017 (Oct 5).
35. Alves RFS, Faerstein E. Desigualdade educacional na ocorrência de obesidade abdominal: Estudo Pró-Saúde [Educational inequality in the occurrence of abdominal obesity: Pró-Saúde Study]. Rev Saúde Pública. 2015;49:65.
36. Moreno-Betancur M, Latouche A, Menvielle G, Kunst AE, Rey G. Relative index of inequality and slope index of inequality: a structured regression framework for estimation. Epidemiology. 2015;26(4):518-27.
37. World Health Organization. Handbook on Health Inequality Monitoring: with a special focus on low- and middle-income countries. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/85345/1/9789241548632_eng.pdf. Accessed in 2017 (Oct 5).
38. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. Ann Fam Med. 2005;3(3):223-8.
39. van den Akker M, Buntix F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol. 1998;51(5):367-75.
40. Britt HC, Harrison CM, Miller GC, Knox SA. Prevalence and patterns of multimorbidity in Australia. Med J Aust. 2008;189(2):72-7.
41. Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol. 2006;16(2):91-104.
42. World Health Organization. Commission on Social Determinants of Health. Health equity through action on the social determinants of health. Geneva: World Health Organization; 2008. Available from: http://apps.who.int/iris/bitstream/10665/43943/1/9789241563703_eng.pdf. Accessed in 2017 (Oct 5).
43. Schäfer I, Hansen H, Schön G, et al. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. BMC Health Serv Res. 2012;12(1):89.
44. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.
45. Hudon C, Fortin M, Poitras M-E, Almirall J. The relationship between literacy and multimorbidity in a primary care setting. BMC Fam Pract. 2012;13(1):33.
46. Reforma da Atenção Primária à Saúde na cidade do Rio de Janeiro - avaliação dos primeiros três anos de Clínicas da Família. Pesquisa avaliativa sobre aspectos de implantação, estrutura, processos e resultados das Clínicas da Família na cidade do Rio de Janeiro. Porto Alegre: OPAS; 2013. Available from: http://www.sbmfc.org.br/media/file/reforma_atencao.pdf. Accessed in 2017 (Oct 5).
47. Starfield B. Atenção primária: equilíbrio entre necessidades de saúde, serviços e tecnologia. Brasília: UNESCO, Ministério da Saúde; 2002. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/atencao_primaria_p1.pdf. Accessed in 2017 (Oct 5).
48. Macinko J, Harris MJ. Brazil's family health strategy--delivering community-based primary care in a universal health system. N Engl J Med. 2015;372(23):2177-81.
49. Promoting health and development: closing the implementation gap. Proceedings of the 7th Global Conference on Health Promotion. October 26-30, 2009. Nairobi, Kenya. Glob Health Promot. 2010;17(2):3-95.

Conflict of interest: None
Sources of funding: None

Date of first submission: July 4, 2017
Last received: August 20, 2017
Accepted: September 10, 2017

Address for correspondence:
Adelson Guaraci Jantsch
Secretaria Municipal de Saúde do Rio de Janeiro, Programa de Residência em Medicina de Família e Comunidade
Rua Evaristo da Veiga, 16 — 4º andar
Rio de Janeiro (RJ) —Brasil
CEP 20211-110
Cel. (+55 21) 97217-3177
E-mail: adelson.smsrio@gmail.com

Proportion of doctors who stayed in the state of Tocantins after finishing medical residency: preliminary results from a cross-sectional study

Leonardo Baldaçara[I], Raquel Prudente de Carvalho Baldaçara[I]

Universidade Federal do Tocantins, Health Department of the State of Tocantins, Palmas (TO), Brazil

[I]MD, PhD. Assistant Professor, Universidade Federal do Tocantins (UFT), Health Department of the State of Tocantins, Palmas (TO), Brazil.

KEY WORDS:
Internship and residency.
Education, medical.
Specialization.
Employment.
Physicians.

PALAVRAS-CHAVE:
Internato e residência.
Educação médica.
Especialização.
Emprego.
Médicos.

ABSTRACT

CONTEXT AND OBJECTIVE: Few studies have assessed the impact of medical residencies on the public healthcare system. The aim here was to assess the number of specialists who remained in the state of Tocantins after finishing the medical residency program during the first two years of the first programs (2013 and 2014).

DESIGN AND SETTING: Cross-sectional and exploratory study conducted at the Federal University of Tocantins in Brazil.

METHODS: All graduates of medical residency programs in Tocantins, of the years 2013 and 2014, were interviewed by telephone and e-mail between May and July 2014.

RESULTS: Information was obtained from 37 graduates from medical residency. Seventeen (50.0%) were working in the state public healthcare system and only six (17.6%) in a municipal service in June 2014. Considering only the 24 doctors who had never worked in the state of Tocantins before their residency, it was observed that two who graduated in 2013 (20.0%) and five who graduated in 2014 (35.7%), i.e. seven out of the total number (29.2%), had established their homes in Tocantins.

CONCLUSIONS: The number of graduates from medical residency who stayed in the state of Tocantins in 2013 and 2014 was small. However, this was related to the absence of other programs for continuation of the specialization. The state healthcare system was primarily responsible for employment of these doctors within public services. On the other hand, hiring by municipal services was extremely low.

INTRODUCTION

The 2011 Medical Demographic Census in Brazil reported that 45% of Brazilian physicians were not specialists.[1] Only 1.9% of medical residency positions and 3.47% of the specialists were located in northern Brazil. Thus, in the state of Tocantins, a lack of professionals working in the public healthcare system was identified, as also in the whole Legal Amazon region.[1] Through the National Program to Support Training of Medical Specialists in Strategic Areas ("Pró-residência"),[2] the first medical residencies were created in this state. The project was supported by the supposition that specialists were more likely to establish themselves in places where they had trained. However, there is no consensus that installation of medical courses (undergraduate or postgraduate level) can allocate new professionals.

The 2013 Medical Demographic Census in Brazil reported that almost two-thirds of doctors remained in the place where they graduated and about a third returned to their hometowns.[3] Regardless of whether professionals graduated in the major centers, these places have greater weight in determining whether doctors stay in the same location.[3]

Interestingly, only a few papers on this topic have been published.[1,3] It is very important to assess the impact of implementing new medical residency programs in priority regions, in order to ascertain whether this type of training stimulates greater numbers of professionals to establish themselves in these locations. Therefore, since Tocantins was the last Brazilian state to open residency programs and there is a national task force to open such postgraduate programs, it is an ideal place to conduct such research.

OBJECTIVE

The aim of this study was to assess the proportion of doctors who stayed in the state of Tocantins after finishing medical residency, after the implementation of the first programs.

METHODS

This was an observational and exploratory cross-sectional study that assessed doctors who finished medical residency programs in the state of Tocantins in the years of 2013 and 2014. Those who did not agree to participate and those who could not be located were excluded. The interviews took place between May and July 2014, which was the fourth year in which the programs had been implemented.

The variables (questions) related to the following: age, gender, medical residency field and year of graduation from residency; whether the subjects were currently (after graduation from residency) working in the state of Tocantins, and if not, why not; whether they were working in a municipal public service; whether they were working in a state public service; whether they were working in the private system in Tocantins; whether they had worked during the residency to supplement their income; current income; and whether before or during the medical residency they had been working in a state or municipal public service.

The interviews took place via email. Subjects who did not respond were contacted by telephone. Among the 37 graduates from residency, 34 participated in the survey. This study was submitted to and approved by the Research Ethics Committee of the Federal University of Tocantins.

Statistical analysis

The data were recorded and analyzed through the IBM SPSS 22.0 software. The variables were presented as absolute numbers and proportions. Subsequently, a comparative analysis was performed using the chi-square test. The significance (α) value selected was ≤ 0.05.

RESULTS

Over the period of this study, the Federal University of Tocantins offered 28 vacancies for medical residency each year: 6 in internal medicine, 6 in general surgery, 6 in pediatrics, 4 in gynecology and obstetrics, 5 in family and community medicine and 1 in psychiatry. However, the occupation rate of these vacancies was low. Over these two years, there were only 37 graduates from 51 vacancies, thus corresponding to an occupancy rate of 72.5%. Information was obtained from 34 of the 37 graduates, i.e. 3 were excluded from the analysis because they could not be contacted. For more details, see **Table 1**.

Employment situation in June 2014

Regarding the employment situation in June 2014, after finishing medical residency, 17 (50.0%) were working in the state of Tocantins and had established their homes there. In comparing the graduates from the years 2013 (7; 46.7%) and 2014 (10; 52.6%), it was observed that the increase in establishment rate was low and not significant ($X^2 = 0.119$; $P = 0.500$). All the specialties were represented among the doctors who had established their homes in Tocantins.

Seventeen (50.0%) were working in the state public healthcare system: seven (46.7%) who had finished their medical residency in 2013 and ten (52.6%) in 2014 ($X^2 = 0.119$; $P = 0.500$). All the specialties were represented among the doctors who were working in this type of system.

However, only six (17.6%) were working in a municipal public healthcare system: three (20.0%) from 2013 and three (15.8%) from 2014 ($X^2 = 0.102$; $P = 0.749$). The specialties of this doctors were: internal medicine, general surgery, pediatrics and community and family medicine. No doctors who had finished residencies were working in the specialties of obstetrics and gynecology or psychiatry, in any municipal network.

The reasons reported by the graduates for not remaining in the state were that they had started attending another residency and that the salary offered was low, compared with other states.

Finally, since these were the first medical residency programs in the state of Tocantins, the subjects were asked whether they were already public employees of the state and whether, through the creation of new courses, they had had the opportunity to

Table 1. Status of graduates from medical residency in the state of Tocantins in July 2014

Variable	2013 n = 15	2014 n = 19	Total n = 34
Age	31 ± 3	30 ± 3	**30.2 ± 3.4**
Male	8 (50.0%)	7 (33.3%)	**15 (40.5%)**
Program			
Internal medicine	8 (50.0%)	8 (38.1%)	**16 (43.2%)**
General surgery	3 (18.8%)	3 (14.3%)	**6 (16.2%)**
Gynecology and obstetrics	0	2 (9.5%)	**2 (5.4%)**
Pediatrics	5 (31.3%)	6 (28.6%)	**11 (29.7%)**
Family and community medicine	0	1 (4.8%)	**1 (2.7%)**
Psychiatry	0	1 (4.8%)	**1 (2.7%)**
Working in the state of Tocantins			
State network	7 (46.7%)	10 (52.6%)	**17 (50.0%)**
Municipal network	3 (20.0%)	3 (15.8%)	**6 (17.6%)**
Private network	7 (46.7%)	10 (52.6%)	**17 (50.0%)**
The current salary is higher than before and/or during residence	4 (26.7%)	7 (36.8%)	**11 (32.4%)**
Doctors who were already civil servants in Tocantins before medical residency	5 (33.3%)	5 (73.7%)	**10 (29.4%)**
Doctors who were new to Tocantins and stayed in the state	2 (20.0%) (n = 10)	5 (35.7%) (n = 14)	**7 (29.2%) (n = 24)**

specialize. In other words, it was assessed whether the trained physicians were already living and working in the state before the medical residency program. It was found that ten (29.4%) were already working in the state of Tocantins and were civil servants. After finishing the medical residency program, they continued in their jobs. A new analysis was then carried out, only among the doctors who had never worked in the state of Tocantins. Out of these 24 subjects, 2 from 2013 (20.0%) and 5 from 2014 (35.7%), i.e. 7 (29.2%) out of the total number were working in the state in June 2014 ($X^2 = 8.697$; $P = 0.404$). In other words, the capacity of medical residency to lead to establishment of new specialists over the short term was low.

Only 4 (26.7%) from 2013, 7 (36.8%) from 2014 and 11 (32.4%) from the total number reported that their current salary was higher than before or during the medical residence.

DISCUSSION

Although Brazil has a national rate of 2.11 doctors per 1,000 inhabitants, the inequalities in the distribution of doctors are enormous. Inequalities exist between different federal states, between state capitals and elsewhere in the respective state, and between groups of municipalities stratified according to population. Data from 2014 showed that northern Brazil (1.09 physician per 1,000 inhabitants) and northeastern Brazil (ratio of 1.3) were below the national rate. However, the highest proportion of doctors per capita (1.51/1,000 inhabitants) in these regions was recorded in Tocantins.[4] Throughout the country, areas away from larger cities show the greatest unevenness of coverage and lack of attendance.[4] Our study corroborates this, in that we noted that most of the specialists who settled in Tocantins stayed in the capital. Even when they went elsewhere in the state, they remained in larger cities.

In previously published data, from 107,114 doctors who graduated from residency in places differing from where they were born, 27,106 (25.31%) were living in the city where they graduated. Among these were some major centers of attraction: about 60% of those who stayed where they graduated from residency remained in seven state capitals, of which five were in southeastern Brazil.[3] The other 40,618 (37.92%), who graduated from residency in locations other than where they were born, were now practicing their activity and/or living in another place, i.e. differing both from where they were born and from where they graduated from residency.[3] In our study, we initially observed an establishment rate of 50%. However, after excluding the confounding factor of already having gained admission as a civil servant in the state of Tocantins before entering the residency, this figure fell to 29.2%.

According to the 2015 census, 41% of physicians in Brazil did not have any specialty. In the country as a whole, the ratio was 1.41 specialists for each generalist.[4] The South had the highest proportion of specialists (2.11) in relation to generalists.[4] At the other extreme, the northern region had the lowest proportion (0.94), thus indicating that for every specialist there was a generalist. In Tocantins, this ratio was 0.80 specialist for each generalist.[4]

In the same way as shown in data from a previous study,[5] the present study showed that there was little demand for and training of specialists in family and community medicine. On the other hand, there was a larger number of trainees within pediatrics.

A previous study[6] that was conducted to identify the characteristics of Memorial University of Newfoundland medical graduates and the predictors that they would continue working in Canada and Newfoundland and Labrador (NL) after residency training concluded that the medical school had made a substantial contribution to the local supply of physicians, such that it had produced over half of the physicians working in that province in 2004. The authors proposed initiatives to increase national and provincial retention of medical graduates: attracting rural students to medical careers, increasing admission of local students and providing incentives for graduates to complete their residency training in the province.[6] In an another study from the same team, it was observed that medical graduates originating from other countries were less likely to work in Canada and NL.[7] On the other hand, another study investigated the factors that family physicians reported as influencing their recruitment and retention. These authors observed that family doctors' decisions to settle and remain in a community were multifactorial. They proposed that the community's educational system and the spouse's needs would have to be directly addressed in order to ensure effective recruitment and retention.[8] A further study assessed factors relating to career longevity that were reported by residency-trained emergency physicians: interactions with residents, higher income, satisfaction with training decisions and board certification in emergency medicine were variables associated with a higher retention rate.[9]

One important question is how to attract doctors to work in primary care and in rural areas. No exact answers have been presented, but the following have been found to be predictive of continued retention in the face of adversity: revision of medical school curricula to encompass current inpatient-oriented training programs;[10] hiring of doctors with residency in family or community practice;[11,12] working in a greater city area;[12] satisfaction with community health centers;[12] and prior resilience under adverse circumstances.[13]

Landry et al.[14] observed that medical training at the undergraduate level did not affect the likelihood of ever or currently practicing in a Canadian province. However, doctors who had been exposed to a training program during postgraduate residency were 5.9 times (95% confidence interval, CI: 2.3-14.9) and 3.2 times (95% CI: 0.9-11.6) more likely, respectively, to practice in

the province than were doctors without postgraduate exposure.[14] Their findings were corroborated by Savageau et al.[12]

In Brazil, a previous study identified the following reasons for difficulty in hiring medical specialists, as pointed out by managers of municipal and state public healthcare systems: lack of graduate professionals, according to the criteria of the Ministry of Education and the Brazilian Medical Association; lack of professionals with the experience required for the work; and the fact that professionals consider that the remuneration levels offered by institutions are low.[15] Comparison between these data and the preliminary results from the present study showed that training more doctors does not lead to more specialists working in the public healthcare system.

We noted that in Tocantins, the main recruitment level was the state, while there was negligible recruitment at municipal level. Among the reasons for difficulties in recruitment given in the abovementioned study,[15] the main reason why these professionals were not working in municipal healthcare services was probably the remuneration, since the state had more attractive proposals. On the other hand, it is possible to speculate that other factors influence professionals' interest: working structure, housing structure and urban facilities.

In a previous study, it was found that few doctors remained in the municipal primary care network and that one of the factors for this was the high turnover of professionals.[16] The municipal administration seemed to contribute directly and strongly towards this phenomenon, as determined by the municipal health bureau. Another 18% was contributed through relationship problems, largely arising from conflicts with management.[16] Improvement in establishing doctors within primary care can be achieved through resolving difficulties relating to the type of employment contract, career plan or lack thereof, remuneration, working hours and questions of political interference.[16] Another author proposed a number of measures to assist in securing doctors within the public system, including a career plan for healthcare professionals and federal employment relationships, which also supports the idea that municipalities have great difficulty in hiring such professionals.[17]

It could be seen that in Tocantins, the medical residency program did not have the capacity to ensure that specialists became established in this state over the short term. We also noticed that there was greater fragility in municipal networks, especially outside of the main urban areas. However, it is important to note that the low attachment rate was attributed to the absence of programs for continuing medical education. In the literature, it has been shown that multiple factors, including education, healthcare system administration priority, workplace conditions, family, income, professional self-interest, and resilience can be related to greater retention of doctors after graduation and medical residency.

CONCLUSION

The number of graduates from medical residency who stayed in the state of Tocantins in the first two years of the program was small, but was related to the absence of other programs for subspecialization. The state network was primarily responsible for employment of these doctors within the public service. On the other hand, hiring by municipal networks was extremely low. A future survey, after five years of implementation of these programs, will review these rates and assess the impact of creation of new medical residency programs.

Finally, it can be assumed that, without an effective state policy for presence in the economic and social development of underserved areas, and without a policy placing greater value on professionals, so as to attract them to public-service careers, the increasing number of doctors will further increase the inequalities.

REFERENCES

1. Scheffer M, Biancarelli A, Cassenote AJF. Demografia Médica no Brasil: dados gerais e descrições de desigualdades. Vol. 1. São Paulo: Conselho Regional de Medicina do Estado de São Paulo e Conselho Federal de Medicina; 2011. Available from: http://portal.cfm.org.br/images/stories/pdf/demografiamedicanobrasil.pdf. Accessed in 2017 (Feb 15).
2. Brasil. Portaria Interministerial nº 1001, de 22 outubro de 2009. Institui o Programa Nacional de apoio a formação de médicos especialistas em áreas estratégicas – Pró-Residência. Diário Oficial da União: Brasília; 2009. Available from: http://portal.mec.gov.br/index.php?option=com_docman&view=download&alias=1682-port-1001&Itemid=30192. Accessed in 2017 (Feb 15).
3. Scheffer M, Cassenote AJF, Biancarelli A. Demografia Médica no Brasil. Vol 2. São Paulo: Conselho Regional de Medicina do Estado de São Paulo e Conselho Federal de Medicina; 2013. Available from: http://www.cremesp.org.br/pdfs/DemografiaMedicaBrasilVol2.pdf. Accessed in 2017 (Feb 15).
4. Scheffer M, Biancarelli A, Cassenote A. Demografia médica no Brasil 2015. São Paulo: Departamento de Medicina Preventiva da Faculdade de Medicina da USP; Conselho Regional de Medicina do Estado de São Paulo; Conselho Federal de Medicina; 2015. Available from: http://www.usp.br/agen/wp-content/uploads/DemografiaMedica30nov2015.pdf. Accessed in 2017 (Feb 15).
5. Ney MS, Rodrigues PHA. Fatores críticos para a fixação do médico na Estratégia Saúde da Família [Critical factors for setting the physician in the Family Health Strategy]. Physis. 2012;22(4):1293-311.
6. Mathews M, Rourke JT, Park A. National and provincial retention of medical graduates of Memorial University of Newfoundland. CMAJ. 2006;175(4):357-60.
7. Mathews M, Park A, Rourke JT. Retention of international medical graduates following postgraduate medical training in Newfoundland and Labrador. Healthc Policy. 2007;3(2):50-7.
8. Crouse BJ. Recruitment and retention of family physicians. Minn Med. 1995;78(10):29-32.

9. Hall KN, Wakeman MA, Levy RC, Khoury J. Factors associated with career longevity in residency-trained emergency physicians. Ann Emerg Med. 1992;21(3):291-7.
10. Linzer M, Slavin T, Mutha S, et al. Admission, recruitment, and retention: finding and keeping the generalist-oriented student. SGIM Task Force on Career Choice in Primary Care and Internal Medicine. J Gen Intern Med. 1994;9(4 Suppl 1):S14-23.
11. Cullen TJ, Hart LG, Whitcomb ME, Rosenblatt RA. The National Health Service Corps: rural physician service and retention. J Am Board Fam Pract. 1997;10(4):272-9.
12. Savageau JA, Ferguson WJ, Bohlke JL, Cragin LJ, O'Connell E. Recruitment and retention of primary care physicians at community health centers: a survey of Massachusetts physicians. J Health Care Poor Underserved. 2011;22(3):817-35.
13. Hancock C, Steinbach A, Nesbitt TS, Adler SR, Auerswald CL. Why doctors choose small towns: a developmental model of rural physician recruitment and retention. Soc Sci Med. 2009;69(9):1368-76.
14. Landry M, Schofield A, Bordage R, Bélanger M. Improving the recruitment and retention of doctors by training medical students locally. Med Educ. 2011;45(11):1121-9.
15. Estação de Pesquisa de Sinais de Mercado em Saúde (ESPM). Avaliação nacional da demanda de médicos especialistas percebida pelos gestores de saúde. Belo Horizonte: Universidade Federal de Minas Gerais; 2009. Available from: https://www.nescon.medicina.ufmg.br/biblioteca/imagem/2466.pdf. Accessed in 2017 (Feb 15).
16. Perpétuo IHO, De Oliveira AC, Ribeiro MM, Rodrigues RB. A categoria profissional dos médicos: fatores condicionantes de sua atração e fixação na Atenção Primária à Saúde em Minas Gerais. Belo Horizonte: Observatório de Recursos Humanos em Saúde do Nig.One/UFMG; 2009.
17. Campos FE, Girardi SN, Machado MH. A fixação de profissionais de saúde em regiões de necessidades [The retention of health professionals in high need areas]. Divulg Saúde para Debate. 2009;44:13-24.

Sources of funding: None
Conflict of interest: None

Date of first submission: December 14, 2016
Last received: January 17, 2017
Accepted: January 28, 2017

Address for correspondence:
Leonardo Baldaçara
Quadra 401 Sul, Avenida Teotônio Segurado, Conjunto 1
Espaço Médico Empresarial, sala 1.006
Plano Diretor Sul — Palmas (TO) — Brasil
CEP 77015-550
Tel. (+55 63) 3217-7288
E-mail: leonardobaldassara@gmail.com

DOI: 10.1590/1516-3180.2017.0272141017

Carotid intima-media thickness in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): a narrative review

Eduardo Henrique Sena Santos[I], Pedro José dos Santos Neto[I], Itamar de Souza Santos[II]

Hospital Universitário (HU), Universidade de São Paulo (USP), São Paulo (SP), Brazil

[I]MD. Physician, Imaging Service, and Researcher, Center for Clinical and Epidemiological Research, Hospital Universitário (HU), Universidade de São Paulo (USP), São Paulo (SP), Brazil.

[II]MD, PhD. Researcher, Center for Clinical and Epidemiological Research, Hospital Universitário (HU), Universidade de São Paulo (USP), and Associate Professor, Department of Internal Medicine, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo (SP), Brazil.

orcid.org/0000-0003-3212-8466

KEY WORDS:
Carotid intima-media thickness.
Atherosclerosis.
Cardiovascular system.
Risk factors.
Cross-sectional studies.

ABSTRACT

BACKGROUND: Carotid intima-media thickness (CIMT), as measured by ultrasound, has been used in large studies as a non-invasive marker for subclinical atherosclerosis. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort of 15,105 civil servants in six Brazilian cities that included CIMT evaluation in its baseline assessment. The aim of the present narrative review was to provide an overview of ELSA-Brasil CIMT articles published up to July 31, 2017.

DESIGN AND SETTING: Narrative review of ELSA-Brasil CIMT studies using baseline assessment data.

METHODS: We searched PubMed for the terms "ELSA-Brasil" and "intima-media". This search yielded 21 published articles using CIMT data from the ELSA-Brasil baseline assessment, which were included in this review. We also present information about intima-media thickness assessment from ongoing onsite reevaluations of the study participants.

RESULTS: Most published studies focused on the association with traditional and novel cardiovascular risk factors. Studies also presented information about the ELSA-Brasil CIMT protocol at baseline and CIMT value distribution in this large sample.

CONCLUSIONS: Analyses on the ELSA-Brasil data led to important insights on CIMT interpretation and physiology. Besides the highlighted contributions which have already been made in this field, new data gathered during the ongoing third onsite assessment will enable investigation of substantially new research questions.

INTRODUCTION

Intima-media thickness (IMT), as measured by ultrasound, has been used in both observational and intervention studies as a non-invasive marker for subclinical atherosclerosis.[1] It has been shown to be associated with cardiovascular risk factors,[2] and to be a predictor of cardiovascular events.[3] Carotid IMT (CIMT) progression over time is used as a surrogate outcome for atherosclerotic disease in clinical trials.[4]

Ultrasound examination allows adequate characterization of carotid walls, is easily executed, is less costly than other imaging techniques, and is widely available. CIMT can be measured by means of B-mode ultrasound, and is defined as the distance between two interfaces: (a) the vascular and intima lumina; and (b) the middle and adventitial layers.[1] Despite many efforts that have been made towards standardizing CIMT definitions, there is no complete consensus in the literature about the best anatomical location, the number of measurements, or which summary of measurements (mean or maximum CIMT) should be used.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)[5,6] is a cohort study on 15,105 civil servants aged 35 to 74 years, in six Brazilian cities (São Paulo, Belo Horizonte, Rio de Janeiro, Porto Alegre, Salvador and Vitória). CIMT data were collected at baseline between August 2008 and December 2010. ELSA-Brasil has one of the largest CIMT datasets among observational studies. As a reference, the ELSA-Brasil CIMT sample size is comparable to large, iconic cohorts that included CIMT evaluation, such as the Atherosclerotic Risk in Communities (ARIC)[7] study and the Multi-Ethnic Study of Atherosclerosis (MESA),[8] and is larger than other important CIMT samples such as the Northern Manhattan (NOMAS)[9] and Rotterdam[10] studies.

The aim of the present narrative review was to provide an overview of articles on CIMT in ELSA-Brasil cohort articles published prior to July 31, 2017, and to summarize the contributions that these studies have made to current knowledge.

METHODS

We searched PubMed for the terms "ELSA-Brasil" and "intima-media" to select the articles included in this review. ELSA-Brasil has a steering committee and a publications and presentations committee.[11] Both are composed of researchers from each ELSA-Brasil investigation site and also keep track of these published papers, which were added to this review.

We classified these articles according to their main objectives, into three subsections: "CIMT protocol and value distributions at ELSA-Brasil baseline", "CIMT and traditional cardiovascular risk factors" and "CIMT and novel cardiovascular risk factors or other conditions". We also present information about IMT assessment from ongoing onsite reevaluations of study participants (ELSA-Brasil Visit 3) and some of the study perspectives for the near future.

RESULTS

We found 21 published articles using CIMT data from the baseline assessment. **Table 1**[12-20] shows the main aims, findings and conclusions of articles focusing on the association with traditional risk factors and **Table 2**[21-32] shows the main aims, findings and conclusions of articles focusing on the association with novel cardiovascular risk factors or other conditions.

DISCUSSION

CIMT protocol and value distributions at ELSA-Brasil baseline

Acquisition of CIMT images in the ELSA-Brasil study complied with the recommendations from the American and Brazilian Societies of Echocardiography. All patients were examined by technicians and/or physicians who had previously been trained and certified for this protocol. The images were obtained using Toshiba Aplio XG ultrasound devices with a linear 7.5 MHz transducer. All images obtained were sent to an examination reading center in São Paulo. To measure CIMT, each common carotid artery (CCA) was identified along its longitudinal axis, using standard brightness and contrast. IMT was calculated automatically using the Medical Imaging Applications software (MIA, Coralville, Iowa, USA), with analysis on three electrocardiographically gated cardiac cycles. Only the proximal far wall of the CCA (1 cm proximally to the carotid bifurcation, with 1 cm length) was measured, and mean and maximum values for each CCA were obtained.[33]

The current Brazilian recommendations for ultrasound evaluation on carotid atherosclerotic disease use the ELSA-Brasil CIMT values as the standard for the Brazilian adult population.[34] These standards are important, because a CIMT value ≥ the 75th percentile for an individual's age, sex and race/ethnicity, and which has been determined from the distribution in his/her reference population, is usually considered indicative of higher subclinical atherosclerosis burden.[35]

Comparing IMT values across cohorts is difficult. Differences in study populations, sample selection, year of recruitment, CIMT protocols and statistical choices influence these comparisons. Considering the context of these limitations, Santos et al.[12] showed that for the same sex, age and race, the CIMT values in ELSA-Brasil were on the whole slightly lower than those in the ARIC study, but were similar to the findings from the German Gutenberg Heart Study.

CIMT and traditional cardiovascular risk factors

The abovementioned article by Santos et al.[12] also assessed some important associations for the Brazilian population. A considerable proportion (43%) of Brazilians reported themselves as "mixed race" in the 2010 national census. This high rate of racial blending, which is also reflected in the ELSA-Brasil sample, cannot be found in other large CIMT samples. These authors concluded that black individuals had higher CIMT values than did white or mixed-race individuals. CIMT values for individuals who self-reported their race as mixed were closer to those found for whites than to those for blacks, after adjustment for age and sex. These findings may reflect constitutional aspects of this measurement, but may also be a marker for racial health inequalities.

New insights about the interpretation of CIMT values came from a 2015 ELSA-Brasil article by Santos et al.[20] The authors found that traditional cardiovascular risk factors explained less than 40% of CIMT variance in the ELSA-Brasil sample, even after adopting analytical strategies to optimize this proportion. This finding is in line with results from other samples, and suggests that there is room to analyze novel risk factors for atherosclerosis in determining CIMT values. It is possible that other factors that are not directly linked to atherosclerosis progression may influence CIMT values. For example, some of these factors may be associated with medial hypertrophy, a condition that may increase CIMT values as well. Identification of these additional factors that are unrelated to atherosclerosis is important for understanding CIMT and its association with cardiovascular risk.

Additional analyses investigating the association between CIMT values and cardiovascular health (CVH) scores at the ELSA-Brasil baseline have corroborated these interpretations. The CVH score was proposed by the American Heart Association in 2010[36] as a tool for measuring CVH in populations. It has well-defined criteria for diet, physical activity, body mass index, smoking, blood pressure, fasting plasma glucose and total cholesterol score. Significant inverse associations were found between CVH scores and CIMT values at the ELSA-Brasil baseline, although some participants with optimum CVH scores had unexpectedly high CIMT values.[13]

Another finding from the ELSA-Brasil data was the close relationship between CIMT values and neck circumference (NC).[17] NC was associated with CIMT values but not with coronary artery

calcium, an alternative marker for subclinical atherosclerosis. Moreover, after adjustment for CCA vessel diameters, this association remained significant, thus suggesting that this does not merely result from larger CCA arteries in individuals with greater NC. One putative explanation for this finding is that there may be a paracrine effect from fatty tissue in the neck, which would influence carotid atherosclerosis but would not have an impact on arteries in other regions.

An association between CIMT values and blood pressure (BP) has been described in the ELSA-Brasil cohort[20] and in other samples.[37] Another two ELSA-Brasil articles have explored additional aspects of this association. Lotufo et al.[18] analyzed data from ELSA-Brasil participants who were using antihypertensive medications. These authors found that those with resistant hypertension (defined as non-controlled BP despite using at least three different classes of antihypertensive medication or controlled BP through using at least

Table 1. ELSA-Brasil studies evaluating the association between carotid intima-media thickness and traditional cardiovascular risk factors

Main aims and associations	Main findings	Main conclusions
Age, sex and race[12]	Median regression slopes: +0.0069 to +0.0079 (per one-year increase in age) AdjB for male sex: +0.036 (P < 0.001) AdjB for mixed race (compared with blacks): -0.030 (P < 0.001) AdjB for white race (compared with blacks): -0.041 (P < 0.001)	CIMT increased with age in all sex and race groups. CIMT was higher in men than in women. Black race was associated with higher CIMT values than those of whites. Mixed-race individuals had intermediate values, but these were closer to those found in whites.
AHA CVH score[13]	AdjB for one-point increase in the CVH score: -0.011 (95% CI: -0.012 to -0.010)	CIMT values were significantly and inversely associated with the CVH score.
Blood pressure variability[14]	Standardized path coefficient from BP variability to residual CIMT (after regression to assess main confounders): +0.046 (P < 0.001)	After minimizing the influence of the main confounders, there was a small but significant association between systolic blood pressure variability and CIMT values.
Glucose levels 10 to 12 years before baseline[15]	AdjB for glucose levels 110-125 mg/dl: +0.028 (95% CI: +0.003 to +0.053) AdjB for incident diabetes: +0.034 (95% CI: +0.015 to +0.053)	Participants with glucose levels between 110 and 125 mg/dl in 1998 had higher CIMT values at the ELSA-Brasil baseline than did those with glucose levels < 100 mg/dl. Participants with incident diabetes during follow-up had higher CIMT values at the ELSA-Brasil baseline than did those without incident diabetes.
HALP[16]	AdjB for HALP: -0.020 (95% CI: -0.042 to +0.003)	CIMT values were not associated with HALP after adjustment for confounders.
Neck circumference[17]	AdjOR for the association between one SD increase in NC and CIMT ≥ 75th percentile Men: 1.66 (95% CI: 1.28-2.14) Women: 1.52 (95% CI: 1.16-1.99)	NC was associated with CIMT but not CAC, thus suggesting that fatty tissues possibly had a local effect.
Resistant hypertension[18]	Prevalence ratio for resistant hypertension associated with higher CIMT values: 3.15 (95% CI: 2.09-4.74)	Individuals with resistant hypertension had higher CIMT values than did those with non-resistant hypertension.
Smoking[19]	AdjB for current smokers: +0.03 (95% CI: +0.02 to +0.04) AdjB for former smokers: +0.01 (95% CI: +0.01 to +0.02) Interaction between age and current smoking: +0.013 (P < 0.001) Interaction between female sex and current smoking: -0.30 (P < 0.001) Interaction between race and current smoking: +0.062 (P = 0.03) Interaction between educational level and current smoking: -0.087 (P = 0.004)	Current and former smokers had higher CIMT values. The association between current smoking and CIMT was stronger among older individuals, males, non-whites and individuals with lower educational levels.
Variance explained by traditional risk factors[20]	R^2 for main models: 0.141 to 0.373 AdjB for one SD increase in blood pressure (all individuals) Men: 0.017 (P < 0.001); women: 0.023 (P < 0.001) AdjB for one SD increase in LDL/HDL ratio (all individuals) Men: 0.009 (P < 0.001); women: 0.009 (P < 0.001) AdjB for one SD increase in NC (all individuals) Men: 0.026 (P < 0.001); women: 0.019 (P < 0.001) AdjB for one SD increase in glycohemoglobin (all individuals) Men: 0.005 (P < 0.05); women: 0.006 (P < 0.01)	Less than 40% of CIMT variance was explained by traditional risk factors. Pulse pressure, LDL/HDL ratio and neck circumference were the most consistent contributors to the main models, while the association with measurements of glucose metabolism was weaker.

95% CI = 95% confidence interval; AdjB = adjusted beta-coefficient; AdjOR = adjusted odds ratio; AHA = American Heart Association; CIMT = carotid intima-media thickness; CVH = cardiovascular health; HALP = hyperalphalipoproteinemia. HDL = high-density lipoprotein; LDL = low-density lipoprotein; NC = neck circumference; SD = standard deviation.

Table 2. ELSA-Brasil studies evaluating the association between carotid intima-media thickness and novel cardiovascular risk factors, and other association studies

Main aims and associations	Main findings	Main conclusions
Adiponectin[21]	AdjOR for the association with CIMT ≥ 75th percentile for a given age, sex and race: Log-transformed adiponectin: 0.78 (95% CI: 0.63-0.97)	Low adiponectin levels were associated with CIMT values in this subgroup, after adjustment for multiple confounders (including body mass index).
Ankle-brachial index[22]	Positive likelihood ratios for high CIMT, using: Highest ankle systolic BP: 2.79 (95% CI: 1.50-5.18) Mean ankle systolic BP: 2.68 (95% CI: 1.74-4.13) Lowest ankle systolic BP: 1.83 (95% CI: 1.42-2.36) Negative likelihood ratios for high CIMT, using: Highest ankle systolic BP: 0.99 (95% CI: 0.99-1.00) Mean ankle systolic BP: 0.99 (95% CI: 0.98-1.00) Lowest ankle systolic BP: 0.98 (95% CI: 0.97-0.99)	Positive likelihood ratios for high CIMT (≥ 75th percentile) were higher when the highest (compared with mean or lowest) ankle systolic BP was used for ankle-brachial index calculation. Negative likelihood ratios for high CIMT (≥ 75th percentile) were similar for all ankle-brachial index calculation strategies.
Cognitive performance[23]	AdjB for delayed word recall test score: -0.433 (95% CI: -0.724 to -0.142)	CIMT values were inversely associated with performance in memory tests.
Cognitive performance[24]	Significant path coefficients for the indirect path between HRV and the TMT-B via HOMA-IR and CIMT: Path coefficient for HRV to HOMA-IR: −0.0942 (P < 0.001) Path coefficient for HOMA-IR to CIMT: +0.0340 (P < 0.0001) Path coefficient for CIMT to TMT-B: +0.1052 (P < 0.0001)	Both insulin resistance and CIMT values mediated the association between heart rate variability and performance in the TMT-B.
Endothelial function[25]	AdjB for the reactive hyperemia index: +0.060 (P = 0.023) AdjB for the mean basal pulse amplitude: +0.010 (P = 0.221)	Endothelial function (according to peripheral arterial tonometry) was inconsistently associated with CIMT. Endothelial dysfunction and CIMT may represent distinct phenomena or different stages of the atherosclerotic process.
HIV infection[26]	AdjB for HIV group: 0.004 (95% CI: -0.006 to +0.014)	Comparing ELSA-Brasil data with information from individuals with HIV infection (mostly undergoing combined antiretroviral therapy), CIMT values did not differ between groups after adjustment for sociodemographic variables and cardiovascular risk factors.
Insulin resistance[27]	AdjOR for the association with CIMT ≥ 75th percentile for a given age, sex and race: One SD increase in HOMA-IR: 1.10 (95% CI: 1.04-1.17)	There was a direct association between insulin resistance and CIMT values, while glucose levels or glycated hemoglobin were not associated with CIMT in the main models. This raised the hypothesis that a direct effect from insulin on atherosclerosis or insulin-promoted medial hypertrophy may be involved.
Mental symptoms[28]	OR for the association with CIMT ≥ 75th percentile for a given age, sex and race: For one SD increase in CIS-R scores: 1.12 (95% CI: 1.06-1.19) For common mental disorder disease: 1.22 (95% CI: 1.07-1.38) For generalized anxiety disorder: 1.19 (95% CI: 1.01-1.41)	Intensity and frequency of mental symptoms, along with generalized anxiety disorder and common mental disorder, were associated with higher CIMT values in full models.
Migraine[29]	AdjB for migraine with aura: -0.01 (95% CI: -0.03 to +0.01) AdjB for migraine without aura: -0.01 (95% CI: -0.02 to +0.01)	Migraine, regardless of the presence of aura symptoms, was not associated with CIMT values after adjustment for confounders.
Socioeconomic mobility[30]	AdjB for downward intergenerational mobility (3 or more levels in a 7-level ladder): +0.013 (P = 0.04) AdjB for stable low social status: +0.012 (P = 0.03)	Downward intergenerational mobility was associated with higher CIMT values, and the more intense the downward mobility was, the more intense this association also was. For intragenerational mobility, individuals with stable low social status had higher CIMT values than did those with stable high social status.
Socioeconomic status[31]	AdjB for low life course socioeconomic position: Men: +0.049 (95% CI: +0.020 to +0.079) Women: +0.031 (95% CI: +0.001 to +0.063)	CIMT values were positively associated with more prolonged exposure to low socioeconomic status (cumulative lifetime socioeconomic position).
Subclinical hypothyroidism[32]	AdjB for subclinical hypothyroidism: +0.010 (95% CI: +0.001 to +0.019) AdjOR for the association with CIMT ≥ 75th percentile for a given age, sex and race: Subclinical hypothyroidism: 1.30 (95% CI: 1.06-1.59)	Subclinical hypothyroidism was associated with CIMT values after adjustment for major confounders.

95% CI = 95% confidence interval; AdjB = adjusted beta-coefficient; AdjOR = adjusted odds ratio; BP = blood pressure; CIMT = carotid intima-media thickness. HOMA-IR = homeostasis model assessment - insulin resistance; OR = odds ratio; SD = standard deviation; TMT-B: trail-making test B.

four different classes of antihypertensive medication) had higher CIMT values than did those with non-resistant hypertension, thus suggesting that a dose-response relationship existed between BP and CIMT. However, this association is not limited to individuals using antihypertensives. Recently, Ribeiro et al.[14] analyzed the association between CIMT values and the patterns in the ten BP measurements that were made during the six-hour baseline visit among ELSA-Brasil participants who were not using antihypertensive drugs. They found that both the central trend (as a weighted mean) of the systolic BP measurements and the systolic BP variability (standard deviation of BP measurements) were associated with CIMT values, after minimizing the influence of other traditional cardiovascular risk factors. This finding suggests that high short-term BP variability has a role in CIMT values and, potentially, in atherosclerosis.

Sitnik et al.[15] analyzed data from a subset of ELSA-Brasil participants at the São Paulo investigation site (N = 1536) who had participated in a workplace screening assessment in 1998 and did not have diabetes at that time. One aim of that study was to evaluate whether glucose levels in 1998 or incident diabetes between assessments would predict CIMT levels at the ELSA-Brasil baseline, 10 to 12 years later. They found that participants with incident diabetes between assessments had higher CIMT values at the ELSA-Brasil baseline. Individuals with glucose levels between 110 mg/dl and 125 mg/dl in 1998 also had higher CIMT values at the ELSA-Brasil baseline than did those with glucose levels below 100 mg/dl, although this association lost significance when individuals who developed diabetes were excluded (P = 0.093).

Elevated high-density lipoprotein cholesterol (HDL-c) levels are typically considered to provide a protective cardiovascular profile. However, there is evidence linking hyperalphalipoproteinemia (HALP), a condition related to very high HDL-c levels, to higher cardiovascular risk,[38] probably due to abnormal HDL-c activity. Using the very large CIMT dataset from the ELSA-Brasil baseline, Laurinavicius et al.[16] found no evidence of higher CIMT values in individuals with HDL-c levels above 90 mg/dl, compared with those with normal HDL levels, in adjusted models.

Recently, Kianoush et al.[19] further explored the association between smoking status and a set of inflammatory and atherosclerotic markers, including CIMT. Besides noting the fact that current and former smokers have higher CIMT values, these authors also suggested that this association is stronger among individuals over 50 years of age, males, non-whites and individuals with lower educational levels. They also found an association between secondhand smoking and CIMT values in models adjusted for age, sex, race and other cardiovascular risk factors. However, this association only maintained borderline significance after adjustment for participants' smoking status and pack-years (P = 0.06).

CIMT and novel cardiovascular risk factors or other conditions

One of the greatest strengths of the ELSA-Brasil cohort is that it enables studies on the effects of social variables on clinical (biological) characteristics. Two ELSA-Brasil studies have focused on the relationship between socioeconomic position and trajectory and CIMT. Camelo et al.[31] evaluated the relationship between CIMT and socioeconomic position over the course of life, as measured by the participants' jobs in their first and current occupations. They found that the association between CIMT and socioeconomic position over the course of life followed a cumulative model, in which CIMT levels were positively associated with more time spent performing jobs of low socioeconomic level. High work stress and passive work were not associated with CIMT, regardless of socioeconomic level. A different analytical strategy was adopted by Guimarães et al.,[30] who also analyzed intergenerational social mobility. In this study, in comparing the change in occupational social class of the head of the household between the participant's occupation at the time of starting to work and his or her current occupation, the participants with downward mobility had higher CIMT values. Moreover, the association was more intense for individuals with greater downward mobility.

Endothelial dysfunction is an important phase of the atherosclerotic process[39] that can be measured using peripheral arterial tonometry (PAT). In a subset of participants at the Minas Gerais investigation site, Lemos et al.[25] evaluated the association between PAT measurements and CIMT values. These authors did not find any consistent associations, thus suggesting that information from PAT and CIMT may be complementary and may represent different phenomena or stages of the atherosclerotic process.

Novel information about CIMT pathophysiology and interpretation resulted from two recent ELSA-Brasil studies. Santos et al.[27] showed that insulin resistance was more strongly associated with CIMT values than with glucose levels, thus suggesting that a hormonal effect on CIMT may exist. This may arise through a direct effect from insulin on the pathogenesis of atherosclerosis. On the other hand, hyperinsulinemia (consequential to insulin-resistant states) may also cause medial hypertrophy, which is included in the intima-media complex. This second hypothesis is further supported by findings from de Almeida-Pititto et al.,[21] who studied the association between CIMT values and serum adiponectin in a subsample of 687 ELSA-Brasil participants in São Paulo aged 35 to 54 years, without diabetes or cardiovascular disease at baseline. Adiponectin also inhibits vascular smooth muscle cell proliferation, and these authors found higher CIMT values in individuals with lower adiponectin levels. In addition, both higher insulin resistance and lower adiponectin levels have been correlated with visceral (including perivascular) adiposity, and we speculate that these may be potential mediators because of their association with higher cardiovascular risk.

Mental disorders and clinical cardiovascular disease are two frequently coexistent conditions, with putative bidirectional causality between them.[40] The ELSA-Brasil baseline forms a good scenario for studying the association between subclinical atherosclerosis and mental disorders, since this baseline assessment included a validated Portuguese-language version of the Clinical Interview Schedule – Revised (CIS-R) questionnaire. CIS-R addresses non-psychotic mental symptoms and enables diagnoses in accordance with the tenth version of the International Classification of Diseases (ICD-10). Santos et al.[28] found that higher CIS-R scores (reflecting more frequent and/or more intense non-psychotic mental symptoms) and a diagnosis of generalized anxiety disorder were associated with higher CIMT values in adjusted models.

Vascular disease is a well-known cause of dementia, but there is conflicting evidence for the association between subclinical carotid atherosclerosis and cognitive decline. Suemoto et al.[23] studied the association between CIMT and cognitive performance among individuals without a medical history of stroke at the ELSA-Brasil baseline. These authors found that there was an association between poorer performance in a memory test (the delayed word recall test) and higher CIMT values, after adjustment for sociodemographic variables, cardiovascular risk factors, diagnosed depression and thyroid function. In addition, Kemp et al.[24] found that CIMT mediates the association between heart rate variability (an index of cardiac autonomic function) and performance in the trail-making test B (an executive cognitive function test), thus further supporting the link between cardiovascular diseases and cognitive performance. One strength of these analyses was that they included a large number of younger adults, a population that had been poorly studied previously.

One continuing controversy is the association between migraine and cardiovascular diseases. Goulart et al.[29] studied the association between a diagnosis of migraine (defined using a validated questionnaire based on the International Headache Society criteria) and subclinical atherosclerosis at the ELSA-Brasil baseline among participants at the São Paulo investigation site. There were no significant associations between migraine (with or without aura) and CIMT values. These results were consistent when subclinical atherosclerosis was defined according to coronary artery calcium (CAC) scores.

Hypothyroidism is associated with a poorer cardiovascular profile,[41] but the effects of subclinical thyroid dysfunction on atherosclerosis is a matter for debate. Peixoto de Miranda et al.[32] studied the association between CIMT values and subclinical hypothyroidism (high thyroid-stimulating hormone with normal free thyroxine levels) at the ELSA-Brasil baseline. In adjusted models, individuals with subclinical hypothyroidism at the baseline had significantly higher CIMT values than did those with normal thyroid function.

Miname et al.[22] compared different protocols for calculating the ankle-brachial index (ABI, a measurement of peripheral artery disease) at the ELSA-Brasil baseline. ABI is based on the ratio of systolic BP measured at the ankle divided by systolic BP measured in the arm. These authors found that when the highest ankle systolic BP was used for ABI calculation, the association with CIMT values was stronger than if they used the mean or lowest ankle systolic BP.

The ELSA-Brasil CIMT data were also used to evaluate the atherosclerotic burden associated with HIV infection. Pacheco et al.[26] compared data from HIV-positive patients who were followed in a cohort in Rio de Janeiro, HIV-negative friends of these subjects, and ELSA-Brasil participants. These authors reported that there were no significant associations between HIV infection status and CIMT values in adjusted models.

ELSA-Brasil Visit 3 and perspectives

The third onsite assessment (Visit 3) of the ELSA-Brasil participants began in early 2017, and is expected to end in 2018. New questionnaires, clinical and laboratory examinations, and CIMT and femoral IMT are included in the Visit 3 protocol. These new data will make it possible to study baseline characteristics that have influenced CIMT progression over an eight-year period. Furthermore, concomitant evaluation of the carotid and femoral arteries may enable greater understanding of how associations with IMT values vary in different arterial beds. Along these lines, some studies[42-44] have shown that cardiovascular risk factors associated with increased CIMT are associated with IMT values at other sites, such as the femoral arteries, but the magnitudes of these associations are heterogeneous. The current approach will allow deeper exploration of relevant scientific questions raised in previous ELSA-Brasil published data, such as the potential paracrine effect of NC on CIMT, for example. On the other hand, other factors that are only weakly associated with CIMT may be more important for determining femoral IMT values.

ELSA-Brasil was designed as a cohort study. One very important research question that longitudinal ELSA-Brasil data may help to answer concerns the extent to which CIMT values and CIMT progression may predict cardiovascular events. Most current data suggest that CIMT values have higher importance than does CIMT progression in cardiovascular risk prediction.[3,45] However, conflicting data exists,[46,47] at least partially due to different study populations and heterogeneous CIMT protocols. In addition, plaque analyses (including total plaque area information) for the common carotid, carotid bulb and internal carotid arteries at the baseline are currently underway. Cross-sectional and longitudinal analyses using these data may be available soon.

CONCLUSIONS

ELSA-Brasil is one of the largest studies with CIMT data. Most published studies have focused on associations with traditional and novel cardiovascular risk factors. Analyses on the ELSA-Brasil data have also led to important insights regarding CIMT interpretation and physiology. In addition to the contributions highlighted here that have already made to this field, new data gathered during the ongoing third onsite assessment will enable investigation of substantially new research questions.

REFERENCES

1. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.
2. Heiss G, Sharrett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol. 1991;134(3):250-6.
3. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.
4. Zanchetti A, Bond MG, Hennig M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation. 2002;106(19):2422-7.
5. Aquino EM, Barreto SM, Bensenor IM, et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol. 2012;175(4):315-24.
6. Schmidt MI, Duncan BB, Mill JG, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75.
7. Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke. 1993;24(9):1297-304.
8. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008;168(12):1333-9.
9. Rundek T, Blanton SH, Bartels S, et al. Traditional risk factors are not major contributors to the variance in carotid intima-media thickness. Stroke. 2013;44(8):2101-8.
10. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. Stroke. 1997;28(12):2442-7.
11. Lotufo PA. Construção do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) Setting up the Longitudinal Study for Adult Health (ELSA-Brasil). Rev Saúde Pública. 2013;47 suppl 2:3-9.
12. Santos IS, Bittencourt MS, Oliveira IR, et al. Carotid intima-media thickness value distributions in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Atherosclerosis. 2014;237(1):227-35.
13. Santos IS, Goulart AC, Pereira AC, Lotufo PA, Benseñor IM. Association between Cardiovascular Health Score and Carotid Intima-Media Thickness: Cross-Sectional Analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) Baseline Assessment. J Am Soc Echocardiogr. 2016;29(12):1207-16.e4.
14. Ribeiro AH, Lotufo PA, Fujita A, et al. Association Between Short-Term Systolic Blood Pressure Variability and Carotid Intima-Media Thickness in ELSA-Brasil Baseline. Am J Hypertens. 2017;30(10):954-60.
15. Sitnik D, Santos IS, Goulart AC, et al. Fasting glucose levels, incident diabetes, subclinical atherosclerosis and cardiovascular events in apparently healthy adults: A 12-year longitudinal study. Diab Vasc Dis Res. 2016;13(6):429-37.
16. Laurinavicius AG, Santos IS, Santos RD, et al. Extremely elevated HDL-cholesterol levels are not associated with increased carotid intima-media thickness: data from ELSA Brasil. J Clin Lipidol. 2016;10(4):898-904.e1.
17. Baena CP, Lotufo PA, Santos IS, et al. Neck circumference is associated with carotid intimal-media thickness but not with coronary artery calcium: Results from The ELSA-Brasil. Nutr Metab Cardiovasc Dis. 2016;26(3):216-22.
18. Lotufo PA, Pereira AC, Vasconcellos PS, et al. Resistant hypertension: risk factors, subclinical atherosclerosis, and comorbidities among adults-the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Clin Hypertens (Greenwich). 2015;17(1):74-80.
19. Kianoush S, Yakoob MY, Al-Rifai M, et al. Associations of Cigarette Smoking With Subclinical Inflammation and Atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health). J Am Heart Assoc. 2017;6(6). pi: e005088.
20. Santos IS, Alencar AP, Rundek T, et al. Low Impact of Traditional Risk Factors on Carotid Intima-Media Thickness: The ELSA-Brasil Cohort. Arterioscler Thromb Vasc Biol. 2015;35(9):2054-9.
21. de Almeida-Pititto B, Ribeiro-Filho FF, Santos IS, et al. Association between carotid intima-media thickness and adiponectin in participants without diabetes or cardiovascular disease of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Eur J Prev Cardiol. 2017;24(2):116-22.
22. Miname M, Bensenor IM, Lotufo PA. Different methods of calculating ankle-brachial index in mid-elderly men and women: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Braz J Med Biol Res. 2016;49(12):e5734.
23. Suemoto CK, Santos IS, Bittencourt MS, et al. Subclinical carotid artery atherosclerosis and performance on cognitive tests in middle-aged adults: Baseline results from the ELSA-Brasil. Atherosclerosis. 2015;243(2):510-5.
24. Kemp AH, López SR, Passos VMA, et al. Insulin resistance and carotid intima-media thickness mediate the association between resting-state heart rate variability and executive function: A path modelling study. Biol Psychol. 2016;117:216-24.

25. Lemos SP, Passos VM, Brant LC, et al. Inconsistent Correlation Between Carotid Artery Intima-Media Thickness and Peripheral Arterial Tonometry: Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Medicine (Baltimore). 2015;94(33):e1403.
26. Pacheco AG, Grinsztejn B, Fonseca Mde J, et al. HIV Infection Is Not Associated with Carotid Intima-Media Thickness in Brazil: A Cross-Sectional Analysis from the INI/ELSA-Brasil Study. PLoS One. 2016;11(7):e0158999.
27. Santos IS, Bittencourt MS, Goulart AC, et al. Insulin resistance is associated with carotid intima-media thickness in non-diabetic subjects. A cross-sectional analysis of the ELSA-Brasil cohort baseline. Atherosclerosis. 2017;260:34-40.
28. Santos IS, Goulart AC, Brunoni AR, et al. Anxiety and depressive symptoms are associated with higher carotid intima-media thickness. Cross-sectional analysis from ELSA-Brasil baseline data. Atherosclerosis. 2015;240(2):529-34.
29. Goulart AC, Santos IS, Bittencourt MS, Lotufo PA, Benseñor IM. Migraine and subclinical atherosclerosis in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Cephalalgia. 2016;36(9):840-8.
30. Guimarães JM, Clarke P, Tate D, et al. Social mobility and subclinical atherosclerosis in a middle-income country: Association of intra- and inter-generational social mobility with carotid intima-media thickness in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Soc Sci Med. 2016;169:9-17.
31. Camelo LV, Giatti L, Chor D, et al. Associations of life course socioeconomic position and job stress with carotid intima-media thickness. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Soc Sci Med. 2015;141:91-9.
32. Peixoto de Miranda ÉJ, Bittencourt MS, Pereira AC, et al. Subclinical hypothyroidism is associated with higher carotid intima-media thickness in cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Nutr Metab Cardiovasc Dis. 2016;26(10):915-21.
33. Mill JG, Pinto K, Griep RH, et al. Afericoes e exames clinicos realizados nos participantes do ELSA-Brasil [Medical assessments and measurements in ELSA-Brasil]. Rev Saúde Pública. 2013;47(supl 2):54-62.
34. Freire CMV, Alcantara ML, Santos SN, et al. Recomendação para a Quantificação pelo Ultrassom da Doença Aterosclerótica das Artérias Carótidas e Vertebrais: Grupo de Trabalho do Departamento de Imagem Cardiovascular da Sociedade Brasileira de Cardiologia – DIC - SBC. Arq Bras Cardiol: Imagem Cardiovasc. 2015;28(no. especial):e1-e64. Available from: http://departamentos.cardiol.br/dic/publicacoes/revistadic/revista/2015/portugues/Numero_Especial/vol28_artigo%20especial_port.pdf. Accessed in 2017 (Oct 31).
35. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93-111; quiz 189-90.
36. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121(4):586-613.
37. Bauer M, Delaney JA, Möhlenkamp S, et al. Comparison of factors associated with carotid intima-media thickness in the Multi-ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR). J Am Soc Echocardiogr. 2013;26(6):667-73.
38. Hirano K, Yamashita S, Kuga Y, et al. Atherosclerotic disease in marked hyperalphalipoproteinemia. Combined reduction of cholesteryl ester transfer protein and hepatic triglyceride lipase. Arterioscler Thromb Vasc Biol. 1995;15(11):1849-56.
39. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114(12):1852-66.
40. Bivanco-Lima D, Santos IS, Vannucchi AMC, Ribeiro MCA. Risco cardiovascular em indivíduos com depressão [Cardiovascular risk in individuals with depression]. Rev Assoc Med Bras (1992). 2013;59(3):298-304.
41. Jabbar A, Pingitore A, Pearce SH, et al. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol. 2017;14(1):39-55.
42. Pasterkamp G, Schoneveld AH, Hillen B, et al. Is plaque formation in the common carotid artery representative for plaque formation and luminal stenosis in other atherosclerotic peripheral arteries? A post mortem study. Atherosclerosis. 1998;137(1):205-10.
43. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. Circulation. 2015;131(24):2104-13.
44. Laclaustra M, Casasnovas JA, Fernández-Ortiz A, et al. Femoral and Carotid Subclinical Atherosclerosis Association with Risk Factors and Coronary Calcium: The AWHS Study. J Am Coll Cardiol. 2016;67(11):1263-74.
45. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. 2012;379(9831):2053-62.
46. Baldassarre D, Veglia F, Hamsten A, et al. Progression of carotid intima-media thickness as predictor of vascular events: results from the IMPROVE study. Arterioscler Thromb Vasc Biol. 2013;33(9):2273-9.
47. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. Stroke. 2011;42(11):3017-21.

Sources of funding: The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) (grant numbers 01 06 0010.00 RS, 01 06

0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP and 01 06 0071.00 RJ). Itamar de Souza Santos is a recipient of a research fellowship from the CNPq (grant number 302364/2016-1) and a research grant from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grant number 2015/17013-3)

Conflicts of interest: The authors report that there were no conflicts of interest

Date of first submission: August 30, 2017
Last received: October 6, 2017
Accepted: October 14, 2017

Address for correspondence:
Itamar de Souza Santos
Centro de Pesquisa Clínica e Epidemiológica do Hospital Universitário da Universidade de São Paulo
Av. Professor Lineu Prestes, 2.565 — 3º andar
São Paulo (SP) – Brasil
CEP 05508-000
Tel. (+55 11) 3091-9300
E-mail: itamarss@usp.br

What do Cochrane systematic reviews say about non-surgical interventions for urinary incontinence in women?

Anderson Adriano Leal Freitas da Costa[I], Igor Martins Vasconcellos[II], Rafael Leite Pacheco[III], Zsuzsanna Ilona Katalin de Jármy Di Bella[IV], Rachel Riera[V]

Discipline of Evidence-Based Health, Escola Paulista de Medicina — Universidade Federal de São Paulo (EPM-Unifesp), São Paulo (SP), Brazil

[I]Undergraduate Medical Student, Escola Paulista de Medicina — Universidade Federal de São Paulo (EPM-Unifesp), São Paulo (SP), Brazil.
orcid.org/0000-0001-6944-103X

[II]Undergraduate Medical Student, Escola Paulista de Medicina — Universidade Federal de São Paulo (EPM-Unifesp), São Paulo (SP), Brazil.
orcid.org/0000-0003-0054-9995

[III]MD. Researcher, Escola Paulista de Medicina — Universidade Federal de São Paulo (EPM-Unifesp), São Paulo (SP), Brazil.
orcid.org/0000-0001-7487-8471

[IV]MD, MSc, PhD. Gynecologist and Adjunct Professor, Department of Gynecology, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-Unifesp), São Paulo (SP), Brazil.
orcid.org/0000-0001-9179-3023

[V]MD, MSc, PhD. Rheumatologist and Adjunct Professor, Discipline of Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-Unifesp), and Assistant Coordinator, Cochrane Brazil, São Paulo (SP), Brazil.
orcid.org/0000-0002-9522-1871.

KEY WORDS:
Review.
Evidence-based medicine.
Therapeutics.
Evidence-based practice.
Urinary incontinence.

ABSTRACT

BACKGROUND: Urinary incontinence is a highly prevalent condition that impacts self-esteem and overall quality of life. Many non-surgical treatment options are available, ranging from pharmacological approaches to pelvic exercises. We aimed to summarize the available evidence regarding these non-surgical interventions.

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

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

RESULTS: We included 20 Cochrane systematic reviews: 4 assessing methods of vesical training, 3 evaluating pharmacological interventions, 4 studying pelvic floor muscle training approaches and 9 aimed at other alternatives (such as urethral injections, weighted vaginal cone use, acupuncture, biostimulation and radiofrequency therapy). The reviews found that the evidence regarding the benefits of these diverse interventions ranged in quality from low to high.

CONCLUSIONS: This review included 20 Cochrane systematic reviews that provided evidence (of diverse quality) for non-pharmacological interventions for patients with urinary incontinence. Moderate to high quality of evidence was found favoring the use of pelvic floor muscle training among women with urinary incontinence. To establish solid conclusions for all the other comparisons, further studies of good methodological quality are needed.

INTRODUCTION

Urinary incontinence (UI) can affect up to 50% of women worldwide.[1] This rate can reach 77% among elderly women living in nursing homes.[2] Additionally, recent research showed that 37.5% of younger women (from 30 to 50 years) in a primary care setting complained of stress incontinence.[3]

Urinary incontinence can be classified into three main types: stress, urge and overflow incontinence. Many women have mixed characteristics of more than one type.[4-6] Identifying the classification can be useful for making decisions regarding therapy, since different therapeutic options are available for each type.[7]

Women presenting stress incontinence (the most common type in younger women) have involuntary leakage of urine relating to increased intra-abdominal pressure (e.g. during physical exercises, sneezing, coughing or laughing) in the absence of a bladder contraction.[4] Urge incontinence (or "overactive bladder with incontinence") is characterized by the urge to void immediately, preceding or accompanied by involuntary loss of urine, which can range from a few drops to full wetting of underwear.[4] It is more common among elderly women and it is related to other clinical situations such as infections or chronic conditions (e.g. neurological disorders or diabetes). Overflow incontinence is characterized by continuous urinary leakage or dripping in the presence of incomplete bladder emptying. Women with overflow incontinence complain of weak or intermittent urinary stream, frequency, hesitancy and nocturia. When the bladder is full, stress leakage can occur or low-amplitude bladder contractions can be induced, thus leading to symptoms similar to urge or stress incontinence. It is caused by bladder obstruction or detrusor hypoactivity.[7] Finally, women with mixed incontinence can present features of both stress and urge incontinence.[4]

It is important to point out that despite the considerable prevalence of UI, it continues to be an underdiagnosed and an undertreated disease: only about a quarter of women with complaints pursue medical care and, of those, less than 50% receive some type of treatment.[8] Persistence of UI has been correlated with poor health outcomes comprising higher risk of urinary infections, sleep disturbances, falls and fractures, and depression.[9,10]

Because UI is a highly prevalent condition, with high impact on quality of life, several treatment options for it are currently available. These options range from pelvic exercises to surgical techniques, including pharmacological therapies and use of local devices.

The aim of the present study was to identify and summarize the evidence from Cochrane systematic reviews (SRs) regarding non-surgical therapeutic options for preventing urinary incontinence and for treating women with this condition.

METHODS

Design and setting

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

Inclusion criteria

Types of study

We included full Cochrane SRs published in the Cochrane Database of Systematic Reviews (CDSR). Protocols for SRs and withdrawn or outdated versions of SRs were not included. There was no limit on publication dates.

Types of participants

The participants considered were women who had been diagnosed with any type of urinary incontinence. We did not take into consideration reviews that included participants of both sexes but did not have any subgroup analyses that considered women alone.

Types of intervention

We considered SRs assessing any non-surgical therapeutic option, whether used in isolation or in combination with each other.

Types of outcomes

We considered any clinical or laboratory outcomes, as evaluated by the authors of the SRs included.

Search for reviews

We conducted a systematic search in the Cochrane Database of Systematic Reviews (CDSR) (via Wiley) on October 18, 2017, sensitively using the MeSH term "urinary incontinence" and all related variants, in titles, abstracts and keywords. The detailed search strategy is presented in **Table 1**.

Selection of reviews

The titles and abstracts were screened by two authors (RLP, AALFC or IMV) independently. The SRs that met the inclusion criteria were selected. Any disagreement was resolved by consulting a senior author (RR).

Presentation of results

The results from the search and the SRs included were presented through a descriptive approach (qualitative synthesis).

RESULTS

Search results

Our search strategy retrieved 106 references and, after screening the titles and abstracts, 31 SRs were preselected. After assessing

Table 1. Search strategy

#1 MeSH descriptor: [Urinary Incontinence] explode all trees
#2 MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
#3 MeSH descriptor: [Urinary Incontinence, Urge] explode all trees
#4 MeSH descriptor: [Urinary Bladder, Overactive] explode all trees
#5 MeSH descriptor: [Urinary Bladder, Neurogenic] explode all trees
#6 (Urinary Incontinence) or (Incontinence, Urinary) or (Urinary Incontinence, Stress) or (Urinary Stress Incontinence) or (Incontinence, Urinary Stress) or (Stress Incontinence, Urinary) or (Urinary Incontinence, Urge) or (Urinary Reflex Incontinence) or (Incontinence, Urinary Reflex) or (Urinary Urge Incontinence) or (Urge Incontinence) or (Incontinence, Urge) or (Nocturnal Enuresis) or (Nighttime Urinary Incontinence) or (Incontinence, Nighttime Urinary) or (Urinary Incontinence, Nighttime) or (Diurnal Enuresis) or (Daytime Urinary Incontinence) or (Incontinence, Daytime Urinary) or (Urinary Incontinence, Daytime) or (Neurogenic Urinary Bladder) or (Bladder, Neurogenic) or (Neurogenic Bladder) or (Urinary Bladder Neurogenic Dysfunction) or (Neurogenic Dysfunction of the Urinary Bladder) or (Neurogenic Urinary Bladder Disorder) or (Neuropathic Bladder) or (Urinary Bladder Disorder, Neurogenic) or (Bladder Disorder, Neurogenic) or (Neurogenic Bladder Disorders) or (Neurogenic Bladder Disorder) or (Urinary Bladder Neurogenesis) or (Neurogenesis, Urinary Bladder) or (Bladder Neurogenesis) or (Neurogenesis, Bladder) or (Neurogenic Urinary Bladder, Atonic) or (Neurogenic Bladder, Atonic) or (Atonic Neurogenic Bladder) or (Neurogenic Urinary Bladder, Spastic) or (Neurogenic Bladder, Spastic) or (Spastic Neurogenic Bladder) or (Neurogenic Urinary Bladder, Uninhibited) or (Neurogenic Bladder, Uninhibited) or (Uninhibited Neurogenic Bladder) or (Overactive Bladder) or (Overactive Urinary Bladder) or (Bladder, Overactive) or (Overactive Detrusor) or (Detrusor, Overactive) or (Overactive Detrusor Function) or (Detrusor Function, Overactive):ti,ab,kw (Word variations have been searched)
#3 #1 or #2 or #3 or #4 or #5 or #6
Filter: in Cochrane Reviews

full texts, 20 reviews[11–30] were found to fulfill our inclusion criteria and were included for qualitative synthesis.

Reviews included

In the following section, we present a brief individual summary of each review included, according to the intervention assessed. For details about the characteristics of the interventions, comparisons, outcomes and quality of evidence,[31] see **Table 2**.

Pharmacological interventions

Adrenergic agonists

This review[11] aimed to assess the effects of adrenergic agonists for stress urinary incontinence (SUI), since these medications may improve bladder neck muscle contraction. The SR included 22 randomized clinical trials (RCTs) (1,099 participants) that assessed phenylpropanolamine, midodrine, norepinephrine, clenbuterol,

Table 2. Characteristics of interventions, comparisons, outcomes and quality of evidence

Pharmacological treatments				
Intervention	**Comparators**	**Urinary incontinence type**	**Main findings**	**GRADE[31]**
Adrenergic agonists[11]	Placebo	Stress	Adrenergic agonists seem to be better for: • reducing the number of pad changes • reducing incontinence episodes • improving symptoms	Not assessed
Estrogen (systemic or local)[12]	Placebo	Not specified	Favors placebo: • Improvement of urinary incontinence (oral systemic estrogen) No difference between groups: • Urinary incontinence episodes over 24 hours • Women with urge incontinence (systemic estrogens) Favors estrogen: • Women with urge incontinence (local estrogen) • Improvement of urinary incontinence (local estrogen) • Improvement of urinary incontinence (local systemic estrogen)	Low Low Moderate Low Moderate Very low
SNRI [13]	Placebo and PFMT	Stress	Favors SNRI: • Higher proportion of participants with symptom improvement Favors control group: • Lower rate of adverse events No difference between groups: • Rate of cure	Not assessed
Adding biofeedback and feedback to other therapies[14]	Other therapies without biofeedback	Urge and mixed	Favors addition of biofeedback: • Women's perception of change in incontinence • Women's satisfaction	Not assessed
Bladder training[15]	Pharmacological therapy, PFMT, biofeedback	Not specified	Favors bladder training: • Better patient perception of cure • Improvement of quality of life	Not assessed
Habit retraining[16]	No intervention	Not specified	No evidence available	Not assessed
Lifestyle interventions[17]	Any other intervention	Not specified	Favors weight loss program: • Patient's subjective impression of improvement No difference between groups: • Cure rates • Frequency of incontinence episodes per week	Low Low Very low
Prompted voiding[18]	No intervention or other behavioral intervention	Not specified	Favors prompted voiding: Lower proportion of hourly checks that were wet Fewer incontinent episodes	Not assessed
Timed voiding[19]	Pharmacological and behavioral therapies	Not specified	No evidence available	Not assessed
Absorbent products[20]	Other absorbent product	Not specified	No evidence available	Not assessed

Continues...

Table 2. Continuation

Pharmacological treatments				
Intervention	**Comparators**	**Urinary incontinence type**	**Main findings**	**GRADE[31]**
Acupuncture[21]	Pharmacological intervention (midodrine)	Stress	Favors acupuncture: • Improvement of symptoms (subjective assessment) No difference between groups: • Cure rate	Not assessed
Mechanical devices[22]	No intervention, sham or other interventions	Not specified	No evidence available	Not assessed
Transurethral radiofrequency collagen denaturation[23]	Sham	Not specified	No difference between groups: • Quality of life • Adverse events • Urinary tract infection	Low
Any intervention[24]	Different intervention, no intervention or placebo	Urinary incontinence after stroke	Favors meclofenoxate (compared with placebo): • Reduction of urinary symptom perception Favors acupuncture (compared with usual care/no intervention): • Reduction in number of participants with incontinence	Not assessed
Urethral injection therapy[25]	Conservative or surgical management	Not specified	Favors injection: • Improvement of incontinence • Quality of life (compared with conservative treatment) Favors surgical treatment: • Symptom improvement	Not assessed
Weighted vaginal cones[26]	No treatment, PFMT, electrostimulation	Stress	Favors vaginal cones: • Incontinence cure (compared with no treatment) No difference between groups: • Subjective cure assessment (compared with pelvic exercises or electrostimulation)	Not assessed
PFMT plus active treatment[27]	Active treatment alone	Stress, urge and mixed	• PFMT plus electrical stimulation versus electrical stimulation alone: no difference between groups regarding cure or improvement of symptoms • PFMT plus heat/steam-generating sheet versus heat/steam sheet alone: benefit of PFMT regarding cure and symptom improvement • PFMT plus vaginal cones versus vaginal cones alone: no difference between groups	Low Moderate Very low
PFMT	No treatment, placebo or sham[28]	Stress, urge and mixed	Favors PFMT: • Cure at end of follow-up • Symptom improvement	High Moderate
	Different approaches for PFMT[29]	Stress, urge and mixed	• Perception of improvement: better with supervision twice a week than once a week No difference between groups: • Perception of improvement: no difference between group supervision and individual supervision, or between direct and indirect methods of PFMT	Not assessed
PFMT in antenatal and postnatal period[30]	No treatment, different approaches for PFMT in antenatal and postnatal period[30]	Not specified	Favors intensive antenatal PFMT: • Incidence of incontinence over first six months after delivery (prevention) Favors intensive postnatal PFMT: • Rate of incontinence 12 months after delivery (treatment)	Not assessed

PFMT = pelvic floor muscle training; SNRI = serotonin-noradrenaline reuptake inhibitor.

*GRADE (Grading of Recommendations Assessment, Development and Evaluation) is a tool for assessing the quality of the body of evidence. Outcomes are classified as presenting high quality of evidence (high confidence that the estimated effect is close to the true effect); moderate quality of evidence (very likely that the estimated effect is close to the real effect, but there is a possibility that it is not); low quality of evidence (confidence in the estimated effect is limited); or very low quality of evidence (the true effect is likely to be substantially different from the estimated effect).

terbutaline, phenylpropanolamine hydrochloride/diphenylpyraline hydrochloride and dabuzalgron (Ro 115-1240). The evidence was very limited and no data were pooled for primary outcomes. The results from single RCTs showed some possible effects from use of adrenergic agonists for improving symptoms and reducing the number of pad changes. However, these results were poorly reported and some important data were missing. Additionally, there is not enough evidence for assessing the effects of these drugs when compared with or combined with other treatments, and hence further larger trials with better quality are needed, to provide stronger evidence. The latest version of this review was published in 2010 and it was declared to be stable considering that some drugs were no longer used and that no new trials were expected.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001842.pub2/abstract.

Estrogens

This review[12] evaluated the effects of estrogens (local or systemic) on post-menopausal women with urinary incontinence (UI), and included 34 RCTs (19,676 participants). From the comparison of estrogen versus placebo/no treatment, the following findings were observed:

- Number of participants with no improvement of urinary incontinence: use of oral systemic estrogens gave rise to a higher number of participants with no improvement (risk ratio [RR] 1.32; 95% confidence interval [CI] 1.17 to 1.48; six RCTs; 6,151 participants; low quality of evidence), while use of local estrogens gave rise to a lower number of participants with no improvement (RR 0.74; 95% CI 0.64 to 0.86; four RCTs; 213 participants; very low quality of evidence).
- Episodes of urinary incontinence over 24 hours: no difference between the groups (mean difference [MD] 0.54; 95% CI -0.5 to 1.57; two RCTs; 82 participants; low quality of evidence).
- Women with urge incontinence: no difference between use of systemic estrogens and placebo (RR 1.05; 95% CI 0.83 to 1.33; two RCTs; 89 participants; moderate quality of evidence), but lower rate with local estrogens than with placebo (RR 0.38; 95% CI 0.15 to 0.99; two RCTS; 90 participants; moderate quality of evidence).
- Women with adverse events: higher rate with use of systemic estrogens (RR 13; 95% CI 1.87 to 90.21; one RCT; 40 participants; low quality of evidence). No difference in adverse events was found with use of local estrogens, compared with placebo (RR 1.33; 95% CI 0.32 to 5.61; two studies; 144 participants; moderate quality of evidence).

The authors concluded that local estrogen treatment may improve UI, but that there was only limited evidence regarding its effects in the post-treatment period and over the long term. However, it was observed that systemic estrogen treatment might worsen incontinence. The data were insufficient to identify the optimal estrogen type and dose, and there was no direct evidence for comparing routes of administration. The risk of endometrial and breast cancer after long-term use of systemic estrogen suggested that this treatment should only be administered for limited periods, especially among women with an intact uterus.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001405.pub3/abstract.

Serotonin-noradrenaline reuptake inhibitors (SNRIs)

This review[13] assessed the effects of a SNRI (duloxetine) for treating women who presented UI. Ten RCTs were included (n = 3,944), and these compared duloxetine with placebo and/or pelvic floor muscle training over periods of three to 12 weeks. The main results were:

- Number of participants with urinary incontinence at the end of the follow-up: no benefits from use of duloxetine 80 mg/day (RR 0.97; 95% CI 0.93 to 1.00; three RCTs; 1,396 participants), 40 mg/day (RR 0.89; 95% CI 0.79 to 1.01; one RCT; 255 participants) and 20 mg/day (RR 0.99; 95% CI 0.89 to 1.09; one RCT; 260 participants).
- Number of participants without improvement during treatment: lower through use of duloxetine 80 mg/day (RR 0.74; 95% CI 0.68 to 0.81; four RCTs; 1,733 participants), 40 mg/day (RR 0.64; 95% CI 0.45 to 0.90; one RCT; 67 participants) and 20 mg/day (RR 0.55; 95% CI 0.40 to 0.75; two RCTs; 160 participants).
- Adverse events: more frequent through use of duloxetine 80 mg/day (RR 1.25; 95% CI 1.14 to 1.36; six RCTs; 1,879 participants).

These results showed that duloxetine could improve symptoms but failed to show any objective improvements in cure rate. The number of participants presenting adverse events was higher in the duloxetine group. Further studies comparing duloxetine and other SNRIs with other treatments are needed in order to reach additional conclusions.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004742.pub2/abstract.

Behavioral methods

Biofeedback

This review[14] assessed the effects of pelvic exercises using different types of feedback and biofeedback among women with urge incontinence and mixed urinary incontinence. Twenty-four trials (n = 1,583) were included and the main results were:

- Pelvic floor muscle training (PFMT) with biofeedback versus PFMT alone: PFMT with biofeedback was statistically significantly better for improving women's perception of change in incontinence (RR 0.75; 95% CI 0.66 to 0.86; seven RCTs; 520 participants) and women's satisfaction (RR 0.65; 95% CI 0.46 to 0.90; three RCTs; 294 participants). There was also a marginally significant result regarding reduction of the number of leakage episodes (MD -0.12; 95% CI -0.22 to -0.01; eight RCTs; 532 participants), but this result might not be clinically relevant.
- PFMT with feedback versus PFMT alone: The group that received feedback had better perception of change in incontinence (RR 0.53; 95% CI 0.37 to 0.78; one RCT; 122 participants) and greater satisfaction (RR 0.33; 95% CI 0.16 to 0.66; one RCT; 166 participants).

Other comparisons were made, but the effects of biofeedback/feedback interventions could not be individually interpreted. The authors of this SR concluded that feedback or biofeedback might provide benefits when added to PFMT in treating urinary incontinence. However, no assessment of quality of evidence was made and no data for safety assessment were provided in the RCTs included.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009252/abstract.

Bladder training

This review[15] assessed bladder training, defined as a behavioral technique in which the patient is trained to resist the first urge to urinate and to refrain from urinating until a planned scheduled time. Eight RCTs (n = 858, predominantly female) were included and the main findings were:

a) Bladder training versus oxybutynin:
   - Patient's perception of cure at six months: better in bladder training group (RR 1.69; 95% CI 1.21 to 2.34; one RCT; 81 participants).
   - Quality of life (general physical measurement): better in bladder training group (weighted mean difference [WMD] 9.00; 95% CI 1.64 to 16.36; one RCT; 57 participants).
b) Bladder training versus imipramine plus flavoxate:
   - Patient's perception of cure immediately after treatment: better in bladder training group (RR 1.50; 95% CI 1.02 to 2.21; one RCT; 50 participants).
c) Bladder training plus pelvic exercises plus biofeedback versus pelvic exercises plus biofeedback:
   - Patient's perception of improvement: better with bladder training (RR 1.18; 95% CI 1.01 to 1.39; one RCT; 125 participants).

All the results of this systematic review were based on poorly reported low-quality RCTs with small sample sizes. The main outcomes were subjective and not pre-specified. Therefore, conclusions regarding the effectiveness and safety of bladder training must await further studies with good methodological and reporting qualities.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001308.pub2/abstract.

Habit retraining

This review[16] assessed the effects of habit retraining, which consists of assistance for toileting provided by a caregiver, with the aim of management of UI. Four RCTs (n = 378) were included, and most of the participants were elderly women who were physically and/or cognitively impaired, and dependent on caregivers. All the RCTs had important methodological limitations and the sparseness of the reported data and the clinical diversity between the studies prevented any quantitative synthesis. Until further studies are available, no judgment regarding the effectiveness and safety of habit retraining can be made.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002801.pub2/full.

Lifestyle interventions

This review[17] assessed the effects of low-cost, non-invasive lifestyle interventions, such as

- dietary changes
- weight loss
- smoking cessation
- physical activity and
- fluid intake in relation to management of UI. Eleven RCTs were included (n = 5,974; mostly female participants).

The following results were found regarding comparison of weight loss programs versus any other intervention:

- Patient's subjective impression of improvement: better in the weight loss program group (RR 1.40; 95% CI 1.14 to 1.71; one RCT; 304 participants; low quality of evidence).
- Cure rates: no difference between groups (RR 1.11; 95% CI 0.91 to 1.37; one RCT; 738 participants; low quality of evidence).
- Frequency of incontinence episodes per week: no difference between groups (RR 0.88; 95% CI 0.78 to 1.00; one RCT; 2,739 participants, very low quality of evidence).

All the trials included were judged to present high risk of bias. Taking into account the quality of the body of evidence relating to weight loss programs and the lack of high quality RCTs, no solid conclusion can be drawn until new studies are available.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003505.pub5/abstract.

Prompted voiding

This review[18] assessed the effects of prompted voiding (a behavioral technique in which the patients receive verbal toilet reminders) for elderly people with UI. Nine RCTs were included (n = 674, the majority of whom were women). The prompted voiding group presented better results for the following outcomes:

- Reduction of the proportion of hourly checks that found wetness (mean difference (MD) 12%; 95% CI -18.79% to -5.21%; one RCT; 148 participants).
- Fewer episodes of incontinence over 24 hours (MD -0.92; 95% CI -1.32 to -0.53; two RCTs; 257 participants).

No statistical difference between the groups were found regarding the number of people with no improvement in wet episodes (OR 0.60; CI 95% 0.29 to 1.26; one RCT; 133 participants). Many of the RCTs included did not provided minimum statistical data for analysis. Also, the clinical outcomes assessed in these RCTs were too diverse and poorly reported. The small sample size and poor methodological quality of the RCTs were an obstacle to drawing any recommendations for practice. Further studies investigating prompted voiding are needed in order to evaluate the safety and effectiveness of this intervention.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002113/abstract.

Timed voiding

This review[19] evaluated the effects of timed voiding for management of UI among elderly women. Two RCTs of poor methodological quality (n = 298) were included and these assessed the effects of timed voiding combined with the usual care (estrogens, propantheline and flavoxate). Therefore, the extent of the effects of timed voiding alone could not be assessed.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002802.pub2/abstract.

Miscellaneous interventions

Absorbent products

This review[20] evaluated the effectiveness of different types of absorbent products for moderate-to-heavy incontinence. Two RCTs were included (n = 185). Fourteen comparisons of absorbent products were made, including disposable insert pads, disposable diapers, T-shaped diapers, disposable pull-ups and washable diapers. The results were sparse and based on only two low-quality RCTs. For most of the comparisons, no difference in the effects was found. Furthermore, for those in which a difference was found, the low quality of the studies precluded any practical recommendation.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007408/abstract.

Acupuncture

This review[21] evaluated the benefits and harms of acupuncture among adults with UI. It included one RCT (n = 60 women) that compared acupuncture versus midodrine:

- Improvement of symptoms (subjective assessment): better with acupuncture (RR 2.20; 95% CI 1.27 to 3.81; one RCT; 60 participants).
- Cure rate: no difference between groups (RR 2.00; 95% CI 0.40 to 10.11; one RCT; 60 participants).

Because this review included only one small head-to-head study with low methodological quality and poor reporting, no conclusions can be reached regarding the efficacy and safety of acupuncture among UI patients.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009408.pub2/abstract.

Mechanical devices

The objective of this review[22] was to assess the use of mechanical devices for management of adult female UI. Eight RCTs were included (n = 787), but no solid conclusions could be drawn because of the lack of reporting and lack of relevant clinical outcome assessment. The RCTs included were poorly reported and no meta-analysis could be performed because of the scarcity and heterogeneous nature of the data. Until further good methodological quality RCTs are published, the uncertainty regarding the effects of mechanical devices in patients with UI will remain unresolved.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001756.pub6/abstract.

Transurethral radiofrequency collagen denaturation (TRCD)

This review[23] evaluated the effects of TRCD in relation to incontinence among women. TRCD is a minimally invasive device-based intervention in which a low-temperature heat is applied via the urethra. One RCT (n = 142) comparing TRCD with a sham group found the following:

- Quality of life: no difference between groups (RR 1.11; 95% CI 0.77 to 1.62; one RCT; 142 participants; low quality of evidence)

- Adverse events: no difference between groups (RR 1.36; 95% CI 0.63 to 2.93; one RCT; 173 participants, low quality of evidence)
- Urinary tract infection: no difference between groups (RR 0.95; CI 95% 0.24 to 3.86; one RCT; 173 participants; low quality of evidence).

The authors concluded that there was insufficient evidence to be able to state that TRCD improves quality of life among patients with UI.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010217.pub2/abstract.

Treatment of UI after stroke

This review[24] evaluated different treatments for UI after stroke and included 12 RCTs (n = 724 participants). The interventions considered were the following: behavioral interventions (three RCTs), specialized professional input interventions (two RCTs), complementary therapy interventions (three RCTs) and pharmacotherapy and hormonal interventions (three RCTs). Most of the RCTs included had small sample sizes and were poorly reported. The main findings were:

- Meclofenoxate versus placebo: reduction in the perception of urinary symptoms through use of meclofenoxate (RR 0.33; 95% CI 0.18 to 0.62; one RCT; 80 participants).
- Acupuncture versus usual care/no intervention: reduction in the number of participants with incontinence after treatment in the acupuncture group (RR 0.44; 95% CI 0.23 to 0.86; three RCTs; 219 participants).

The authors concluded that there was insufficient evidence to guide UI management after stroke.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004462.pub3/abstract.

Urethral injection therapy

This review[25] evaluated the efficacy and safety of injections of periurethral or transurethral bulking agents that had the aim of creating artificial cushioning in the area around the urethra. It included 14 RCTs (n = 2,004 women) and the main results were:

- Injection versus conservative treatment: the injection treatment group had a higher number of participants with improvement of continence than did the conservative treatment group (RR 0.70; 95% CI 0.52 to 0.94; one RCT; 45 participants) and it achieved a statistically significant improvement of quality of life (MD 0.54; 95% CI 0.16 to 0.92; one RCT; 45 participants).
- Injection versus surgical management: the surgical group had higher rates of symptom improvement in two trials: RR 4.77; 95% CI 1.96 to 11.64; one RCT; 45 participants in one study; and RR 1.69; 95% CI 1.02 to 2.79; one RCT; 54 participants in the other study.

The results from the remaining RCTs included were poorly reported and no data could be pooled because of the lack of relevant outcome results and because of the heterogeneity between studies. Until further high-quality studies are available, the benefits of urethral injection therapy in patients with urinary incontinence will remain a matter that needs to be resolved.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003881.pub4/abstract.

Weighted vaginal cones

This review[26] evaluated the efficacy and safety of use of weighted vaginal cones for women with urinary incontinence and it included 23 RCTs (n = 1,806). The following results were found:

- Weighted vaginal cones versus no treatment: the intervention group had a lower number of patients with urinary incontinence at the end of the follow-up (RR 0.84; 95% CI 0.76 to 0.94; four RCTs; 375 participants).
- Weighted vaginal cones versus pelvic exercises: no difference between the groups regarding subjective assessment of cure (RR 1.01; 95% CI 0.91 to 1.13; five RCTs; 338 participants).
- Weighted vaginal cones versus electrostimulation: no difference between the groups regarding subjective assessment of cure (RR 1.26; 95% CI 0.85 to 1.87; three RCTs; 151 participants).

The authors concluded that these findings suggested that cones were a better option than no treatment. However, no assessment of the quality of the body of evidence was made. More high-quality trials are necessary in order to fully evaluate the possible benefits and adverse events of use of weighted cones for treatment of urinary incontinence, preferably with larger sample sizes and using standard relevant outcomes.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002114.pub2/abstract.

Pelvic floor muscle training (PFMT) interventions

Four reviews[27–30] assessed the efficacy and safety of PFMT for management of UI (stress, urge and mixed) in women.

One review[27] compared PFMT combined with active treatment versus the same active treatment alone, and included 13 trials (n = 1,164). The key outcomes considered by the review authors were not assessed in the majority of the RCTs included. The main results reported were:

- PFMT plus electrical stimulation versus electrical stimulation alone: no difference between groups regarding cure or improvement of symptoms (RR 2.06; 95% CI 0.79 to 5.38; two RCTs; 56 participants; very low quality of evidence).
- PFMT plus heat and steam-generating sheet *versus* heat and steam-generating sheet alone: the group that received PFMT had higher likelihood of participants presenting cure or symptom improvement (RR 2.38; 95% CI 1.19 to 4.73; one RCT; 74 participants; moderate quality of evidence).
- PFMT plus vaginal cones versus vaginal cones alone: no difference between groups (RR 1.27; 95% CI 0.94 to 1.71; one RCT; 34 participants; very low quality of evidence).

The adverse events were only evaluated in one RCT in which PFMT in combination with drug therapy was assessed, and this did not find any statistical difference (RR 0.84; 95% CI 0.45 to 1.60; one RCT; 162 participants; very low quality of evidence). In the light of these findings, the authors concluded that there was insufficient evidence to state what the effects of addition of PFMT to treatments for urinary incontinence were.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010551.pub3/abstract.

The second review[28] included 21 RCTs (n = 1,281 participants) that compared PFMT with no treatment, placebo or sham. The main results were:

- Cure at the end of the follow-up: higher likelihood in the PFMT group (RR 8.38; 95% CI 3.68 to 19.07; four RCTs; 165 participants; high quality of evidence).
- Symptom improvement: higher likelihood in the PFMT group (RR 17.33; 95% CI 4.31 to 69.64; two RCTs; 121 participants; moderate quality of evidence).

The authors concluded that these findings supported a recommendation to use PFMT as first-line conservative therapy for women with urinary incontinence.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005654.pub3/abstract.

Other comparisons were made, but the data were sparse and based on low-quality RCTs. Moreover, there was no assessment of the quality of the body of evidence for any comparison. The authors concluded that currently there was insufficient evidence to make any strong recommendations about the best approach to use for PFMT.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009508/abstract.

The fourth review[30] assessed the effects of PFMT for prevention and treatment of UI among antenatal and postnatal women. Twenty-two RCTs (n = 8,485) were included and the main findings were:

- Incidence of incontinence over the first six months after delivery (prevention): lower likelihood among pregnant women with intensive antenatal PFMT than among those with postnatal PFMT (RR 0.71; 95% CI 0.54 to 0.95; five RCTs; 673 participants).
- Rate of incontinence 12 months after delivery (treatment): no difference in likelihood between pregnant women with intensive postnatal PFMT and those who received intensive antenatal PFMT (RR 0.60; 95% CI 0.35 to 1.03; three RCTs).

The authors concluded that there was some evidence to support the use of PFMT among women who were having their first baby, to prevent UI over the first six months after delivery. However, there was no appraisal of the quality of the evidence, and the clinical and methodological heterogeneity among the studies included prevented other pooled analyses.

For further details, refer to the original abstract, available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007471.pub2/abstract.

DISCUSSION

This review included 20 Cochrane systematic reviews that assessed non-surgical interventions for women with urinary incontinence. The studies included evaluated pharmacological interventions (three SRs), behavioral interventions (six SRs), miscellaneous interventions (seven SRs) and pelvic floor muscle training interventions (four SRs).

Despite the considerable numbers of studies included in many of these SRs, most of them were poorly reported with low methodological quality, which compromised confidence in the data synthesis. However, the quality of the body of evidence was only assessed in five SRs.[12,17,23,27,28] Since the publication of the GRADE initiative,[31] evaluation of the quality of the evidence synthetized has become recommended and, for further updates, this needs to be a priority.[31]

Regarding the clinical implications, the only systematic reviews that presented moderate to high quality of evidence were those relating to use of pelvic floor muscle training among women with urinary incontinence. On the other hand, the quality of evidence reported was very low to moderate in relation to use of estrogen for treating and preventing urinary incontinence. Moreover, the outcomes reported from all other interventions presented very low to low quality of evidence. The results presented in **Table 2** may provide some guidance for using some of the interventions evaluated in this overview of systematic reviews, but most of the findings may change through future studies.

Regarding the implications for further research, our results suggest that it is important to plan and conduct randomized controlled

trials assessing non-pharmacological interventions for women with urinary incontinence strictly in accordance with rigorous protocols. The trial protocols need to be published before the study begins and the results need to be presented in accordance with the CONSORT guidelines.[32]

CONCLUSION

This review included 20 Cochrane systematic reviews that provided evidence ranging in quality from unknown to high, in relation to non-pharmacological interventions for patients with urinary incontinence. Moderate to high quality of evidence favoring use of pelvic floor muscle training among women with urinary incontinence was found. To establish solid conclusions for all the other comparisons, further studies of good methodological quality are needed.

REFERENCES

1. Minassian VA, Stewart WF, Wood GC. Urinary incontinence in women: variation in prevalence estimates and risk factors. Obstet Gynecol. 2008;111(2 Pt 1):324-31. doi: 10.1097/01.AOG.0000267220.48987.17.
2. Offermans MP, Du Moulin MF, Hamers JP, Dassen T, Halfens RJ. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. Neurourol Urodyn. 2009;28(4):288-94. doi: 10.1002/nau.20668.
3. Ng SF, Lok MK, Pang SM, Wun YT. Stress urinary incontinence in younger women in primary care: prevalence and opportunistic intervention. J Women's Health (Larchmt). 2014;23(1):65-8. doi: 10.1089/jwh.2013.4382.
4. Abrams P, Andersson KE, Birder L, et al. Fourth international consultation on incontinence recommendations of the international scientific committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn. 2010;29(1):213-40. doi: 10.1002/nau.20870.
5. Holroyd-Leduc JM, Tannenbaum C, Thorpe KE, Straus SE. What type of urinary incontinence does this woman have? JAMA. 2008;299(12):1446-56. doi: 10.1001/jama.299.12.1446.
6. Barry MJ, Link CL, McNaughton-Collins MF, McKinlay JB; Boston Area Community Health (BACH) Investigators. Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int. 2008;101(1):45-51. doi: 10.1111/j.1464-410X.2007.07191.x.
7. UpToDate. Evaluation of women with urinary incontinence. Available from: https://www.uptodate.com/contents/evaluation-of-women-with-urinary-incontinence. Accessed in 2017 (Dec 21).
8. Minassian VA, Yan X, Lichtenfeld MJ, Sun H, Stewart WF. The iceberg of health care utilization in women with urinary incontinence. Int Urogynecol J. 2012;23(8):1087-93. doi: 10.1007/s00192-012-1743-x.
9. Wagner TH, Hu T, Bentkover J, et al. Health-related consequences of overactive bladder. Am J Manag Care. 2002;8(19 Suppl):S598-607. PMID: 12516954.
10. Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. Am J Manag Care. 2000;6(11 Suppl):S574-9. PMID: 11183900.
11. Alhasso AA, Glazener CM, Pickard R, N'Dow JM. Adrenergic drugs for urinary incontinence in adults. Cochrane Database Syst Rev. 2005;(3):CD001842. doi: 10.1002/14651858.CD001842.pub2.
12. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2012 Oct 17;10:CD001405. doi: 10.1002/14651858.CD001405.pub3.
13. Mariappan P, Ballantyne Z, N'Dow JM, Alhasso AA. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Cochrane Database Syst Rev. 2005;(3):CD004742. doi: 10.1002/14651858.CD004742.pub2.
14. Herderschee R, Hay-Smith EJC, Herbison GP, Roovers JP, Heineman MJ. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev. 2011;(7):CD009252. doi: 10.1002/14651858.CD009252.
15. Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(1):CD001308. doi: 10.1002/14651858.CD001308.pub2.
16. Ostaszkiewicz J, Chestney T, Roe B. Habit retraining for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(2):CD002801. doi: 10.1002/14651858.CD002801.pub2.
17. Imamura M, Williams K, Wells M, McGrother C. Lifestyle interventions for the treatment of urinary incontinence in adults. Cochrane Database Syst Rev. 20152;(12):CD003505. doi: 10.1002/14651858.CD003505.pub5.
18. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2000;(2):CD002113. doi: 10.1002/14651858.CD002113.
19. Ostaszkiewicz J, Johnston L, Roe B. Timed voiding for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(1):CD002802. doi: 10.1002/14651858.CD002802.pub2.
20. Fader M, Cottenden AM, Getliffe K. Absorbent products for moderate-heavy urinary and/or faecal incontinence in women and men. Cochrane Database Syst Rev. 2008;(4):CD007408. doi: 10.1002/14651858.CD007408.
21. Wang Y, Zhishun L, Peng W, Zhao J, Liu B. Acupuncture for stress urinary incontinence in adults. Cochrane Database Syst Rev. 2013;(7):CD009408. doi: 10.1002/14651858.CD009408.pub2.
22. Lipp A, Shaw C, Glavind K. Mechanical devices for urinary incontinence in women. Cochrane Database Syst Rev. 2014;(12):CD001756. doi: 10.1002/14651858.CD001756.pub6.
23. Kang D, Han J, Neuberger MM, et al. Transurethral radiofrequency collagen denaturation for the treatment of women with urinary incontinence. Cochrane Database Syst Rev. 2015;(3):CD010217. doi: 10.1002/14651858.CD010217.pub2.
24. Thomas LH, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. Cochrane Database Syst Rev. 2008;(1):CD004462. doi: 10.1002/14651858.CD004462.pub3.

25. Kirchin V, Page T, Keegan PE, et al. Urethral injection therapy for urinary incontinence in women. Cochrane Database Syst Rev. 2017;7:CD003881. doi: 10.1002/14651858.CD003881.pub4.
26. Herbison GP, Dean N. Weighted vaginal cones for urinary incontinence. Cochrane Database Syst Rev. 2013;(7):CD002114. doi: 10.1002/14651858.CD002114.pub2.
27. Dumoulin C, Hay-Smith EJ, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014;(5):CD005654. doi: 10.1002/14651858.CD005654.pub3.
28. Hay-Smith EJ, Herderschee R, Dumoulin C, Herbison GP. Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev. 2011;(12):CD009508. doi: 10.1002/14651858.CD009508.
29. Boyle R, Hay-Smith EJ, Cody JD, Mørkved S. Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. Cochrane Database Syst Rev. 2012;10:CD007471. doi: 10.1002/14651858.CD007471.pub2.
30. Ayeleke RO, Hay-Smith EJ, Omar MI. Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women. Cochrane Database Syst Rev. 2015;(11):CD010551. doi: 10.1002/14651858.CD010551.pub3.
31. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. doi: 10.1136/bmj.328.7454.1490.
32. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi: 10.1136/bmj.c869.

Source of funding: None
Conflict of interest: None

Date of first submission: December 1, 2017
Last received: December 20, 2017
Accepted: December 20, 2017

Address for correspondence:
Rafael Leite Pacheco
Programa de Pós-graduação em Saúde Baseada em Evidências, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (Unifesp)
Rua Botucatu, 740 – 3º andar
São Paulo (SP) — Brasil
CEP 04023-900
Cel. (+ 55 19) 99849-4045
E-mail: rleitepacheco@hotmail.com

DOI: 10.1590/1516-3180.2016.0299071216

Bariatric surgery in individuals with severe cognitive impairment: report of two cases

Cirurgia bariátrica em indivíduos com déficits cognitivos graves: relato de dois casos

Everton Cazzo[I], Martinho Antonio Gestic[II], Murillo Pimentel Utrini[III], Felipe David Mendonça Chaim[IV], Elaine Cristina Cândido[V], Luciana Bueno da Silveira Jarolavsky[VI], Ana Maria Neder de Almeida[VII], José Carlos Pareja[VIII], Elinton Adami Chaim[IX]

Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil

[I]MD, MSc, PhD. Assistant Lecturer, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.

[II]MD, MSc. Assistant Lecturer, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.

[III]MD. Assistant Lecturer, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-Unicamp), Campinas (SP), Brazil.

[IV]MD, MSc. Attending Physician, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.

[V]BSc. Attending Nurse, Bariatric Surgery Outpatient Service, Hospital de Clínicas da Universidade Estadual de Campinas (HC-UNICAMP), Campinas (SP), Brazil.

[VI]BSc. Head Nurse, Bariatric Surgery Outpatient Service, Hospital de Clínicas da Universidade Estadual de Campinas (HC-UNICAMP), Campinas (SP), Brazil.

[VII]BSc. Attending Psychologist, Bariatric Surgery Outpatient Service, Hospital de Clínicas da Universidade Estadual de Campinas (HC-UNICAMP), Campinas (SP), Brazil.

[VIII]MD, PhD. Associate Professor, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.

[IX]MD, MSc, PhD. Full Professor, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.

KEY WORDS:
Prader-Willi syndrome.
Down syndrome.
Bariatric surgery.
Obesity.
Intellectual disability.

PALAVRAS-CHAVE:
Síndrome de Prader-Willi.
Síndrome de Down.
Cirurgia bariátrica.
Obesidade.
Deficiência intelectual.

ABSTRACT

CONTEXT: Bariatric surgery has become the gold-standard treatment for refractory morbid obesity. Obesity is frequently associated with certain syndromes that include coexisting cognitive deficits. However, the outcomes from bariatric surgery in this group of individuals remain incompletely determined.

CASE REPORT: A 25-year-old male with Prader-Willi syndrome, whose intelligence quotient (IQ) was 54, was admitted with a body mass index (BMI) of 55 kg/m^2, associated with glucose intolerance. He underwent the Scopinaro procedure for biliopancreatic diversion, with uneventful postoperative evolution, and presented a 55% loss of excess weight one year after the surgery, with resolution of glucose intolerance, and without any manifestation of protein-calorie malnutrition. A 28-year-old male with Down syndrome, whose IQ was 68, was admitted with BMI of 41.5 kg/m^2, associated with hypertension. He underwent Roux-en-Y gastric bypass, with uneventful postoperative evolution. He presented a 90% loss of excess weight one year after the surgery, with resolution of the hypertension.

CONCLUSION: Bariatric surgery among individuals with intellectual impairment is a controversial topic. There is a tendency among these individuals to present significant weight loss and comorbidity control, but less than what is observed in the general obese population. The severity of the intellectual impairment may be taken into consideration in the decision-making process regarding the most appropriate surgical technique. Bariatric surgery is feasible and safe among these individuals, but further research is necessary to deepen these observations.

RESUMO

CONTEXTO: A cirurgia bariátrica tornou-se o tratamento padrão ouro para a obesidade mórbida refratária. A obesidade está frequentemente associada a certas síndromes nas quais também coexistem déficits cognitivos, entretanto, os resultados da cirurgia bariátrica nesse grupo de indivíduos ainda não foram completamente determinados.

RELATO DE CASO: Um homem de 25 anos com síndrome de Prader-Willi, cujo quociente de inteligência (QI) era estimado em 54, foi admitido com índice de massa corporal (IMC) de 55 kg/m^2, associado com intolerância à glicose. Foi submetido a uma derivação biliopancreática à Scopinaro, com evolução pós-operatória sem complicações significativas. Apresentou perda de 55% do excesso de peso um ano após a cirurgia, com resolução da intolerância à glicose, sem manifestação de desnutrição proteico-calórica. Outro paciente, homem de 28 anos com syndrome de Down, cujo QI era de 68, foi admitido com IMC de 41,5 kg/m^2, associado a hipertensão arterial. Foi submetido ao *bypass* gástrico em Y de Roux, com evolução pós-operatória sem complicações. Apresentou perda de 90% do excesso de peso após um ano e resolução da hipertensão.

CONCLUSÃO: A cirurgia bariátrica em indivíduos com déficits intelectuais é um tópico controverso. Existe uma tendência entre esses indivíduos de apresentar perda de peso e controle de comorbidades significativos, porém menores que os observados na população obesa geral. A gravidade do déficit intelectual pode ser considerada no processo de decisão sobre a técnica cirúrgica mais adequada. A cirurgia bariátrica é factível e segura nesse grupo de indivíduos. Porém, mais estudos são necessários para aprofundar estas observações.

INTRODUCTION

Bariatric surgery has become the standard treatment option for refractory morbid obesity. The observed overall impact of this surgery on obese patients has been found to be 40% regarding long-term reduction in mortality, 56% for coronary heart disease, 92% for diabetes complications and 60% for any type of cancer.[1,2]

Obesity and its related comorbidities are common among individuals with cognitive impairment, but the outcomes from bariatric surgery in this singular group remain uncertain.[3-7] The majority of bariatric programs exclude patients with intellectual and/or developmental disabilities, from surgical indication. Only 6.2% of programs have not considered severe levels of impairment, i.e. intelligence quotient (IQ) of 50–70, to be a contraindication.[8] Moreover, current guidelines emphasize the importance of a clear understanding among patients regarding the risks, benefits, outcomes and alternatives to surgery. This ability to give consent is possibly compromised in cognitively impaired individuals.[6]

OBJECTIVE

To report the cases of two individuals with severe non-acquired cognitive impairment who underwent bariatric surgery.

CASE REPORT

Case 1

EGR, a 25-year-old male with Prader-Willi syndrome, whose IQ was 54, presented with a body mass index (BMI) of 55 kg/m^2, associated with impaired glucose tolerance and walking disability. He underwent the Scopinaro procedure for biliopancreatic diversion, with uneventful postoperative evolution. The main caregiver during the postoperative phase was his mother, who chose to perform caregiving functions full-time.

One year after the surgery, he presented BMI of 38.5 kg/m^2, i.e. a 55% loss of excess weight. His impaired glucose tolerance had been resolved; his ability to walk had developed; and he did not present any features of malnutrition. No cognitive evaluation test was performed after the surgery. Two years after the surgery, the family chose to leave the patient at a part-time non-profit institution for intellectually disabled people.

Case 2

JLC, a 28-year-old male with Down syndrome, with IQ of 68, presented with a BMI of 41.5 kg/m^2, associated with hypertension. He underwent Roux-en-Y gastric bypass, with uneventful postoperative evolution. The main caregivers during the postoperative phase were his mother and sister, who both chose to perform caregiving functions full-time.

One year after the surgery, he presented BMI of 26.7 kg/m^2, i.e. a 90% loss of excess weight, with resolution of his hypertension. No cognitive evaluation test was performed after the surgery. One year after the surgery, the patient began to work part-time at a grocery store.

Table 1 summarizes the main clinical and laboratory outcomes relating to these two individuals.

DISCUSSION

Bariatric surgery among individuals with severe intellectual impairment remains a controversial topic. There is a tendency

Table 1. Outcomes from bariatric surgical procedures on two individuals with severe cognitive impairment

Patient	EGR	JLC
Syndrome	Prader-Willi	Down
Surgical technique	Biliopancreatic diversion	Roux-en-Y gastric bypass
Preoperative BMI (kg/m^2)	55	41.5
Postoperative BMI (kg/m^2)	38.5	26.7
% EWL	55%	90%
Comorbidity outcomes	Resolution of impaired glucose tolerance and improvement of gait impairment	Resolution of hypertension
Preoperative glucose (mg/dl)	123	96
Postoperative glucose (mg/dl)	81	75
Preoperative triglycerides (mg/dl)	212	148
Postoperative triglycerides (mg/dl)	126	74
Preoperative LDL-c (mg/dl)	145	179
Postoperative LDL-c (mg/dl)	99	74
Preoperative HDL-c (mg/dl)	25	29
Postoperative HDL-c (mg/dl)	37	52

BMI = body mass index; % EWL = percentage of excess weight loss; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol.

among these individuals to present significant weight loss and comorbidity control, but less than what is observed among individuals without cognitive impairment.[9]

A review of the literature on this subject was conducted through an online search for the Medical Subject Headings (MeSH) terms Prader-Willi syndrome, Down syndrome, intellectual disability and bariatric surgery, in MEDLINE (via PubMed) and LILACS (via BVS) (**Table 2**). After extensive online research, we identified six case series, five case reports, one matched-cohort study and one scoping review that evaluated bariatric surgery among individuals with severe cognitive impairment. **Table 3**[6,7,9-19] summarizes the main articles found and their respective characteristics and levels of evidence, according to the Oxford classification.

Interestingly, despite the much higher frequency of Down syndrome in the general population (one per 700 to 1,000 newborns), we observed that the vast majority of the studies included individuals with Prader-Willi syndrome, which occurs less commonly (1 per 10,000 to 25,000 newborns).[20] In fact, only the study by Daigle et al.[7] included two individuals with Down syndrome. Whether this finding is due to non-treatment of these individuals or underreporting of the treated cases remains to be determined.

There is a strong necessity for social support within this group of individuals, especially regarding family support and caregivers. Since these individuals do not present the capacity to understand and formally consent to such procedures, the main caregivers need to be directly asked about this topic. Social support must be emphasized postoperatively, to avoid loss of adherence to the long-term follow-up.[6-8]

Since there is no consensus regarding which procedure is most appropriate, the severity of intellectual impairment may be taken

Table 2. Database search results for bariatric surgery among individuals with severe cognitive impairment, conducted on November 14, 2016

Electronic databases	Search strategies	Results
MEDLINE (PubMed)	((Prader-Willi Syndrome) OR (Down Syndrome) OR (Intellectual Disability)) AND (Bariatric surgery)	6 case series 5 case reports 1 matched-cohort study 1 review
LILACS (BVS)	((Prader-Willi Syndrome) OR (Síndrome de Prader-Willi) OR (Down Syndrome) OR (Síndrome de Down) OR (Intellectual Disability) OR (Discapacidad Intelectual) OR (Deficiência Intelectual)) AND ((Bariatric surgery) OR (Cirugia Bariátrica) OR (Cirurgia Bariátrica))	3 case series 4 case reports 1 matched-cohort study 1 review

Table 3. Main studies on bariatric surgery among individuals with severe cognitive impairment

Authors	Methodology	N	Level of evidence	Type of impairment	Surgical technique
Algahtani et al.[9]	Matched-control	24	3b	Prader-Willi Syndrome	Sleeve gastrectomy
Daigle et al.[6]	Case series	6	4	2 – Down syndrome 4 – unknown	2 – Roux-en-Y gastric bypass 3 – Sleeve gastrectomy 1 – Gastric banding
Heinberg et al.[7]	Case report	1	4	Unknown	Roux-en-Y gastric bypass
Musella et al.[10]	Case series	3	4	Prader-Willi syndrome	Mini-gastric bypass
Fong et al.[11]	Case series	3	4	Prader-Willi syndrome	2 – Sleeve gastrectomy 1 – Mini-gastric bypass
Kobayashi et al.[12]	Case report	1	4	Prader-Willi syndrome	Roux-en-Y gastric bypass
Braghetto Miranda et al.[13]	Case report	1	4	Prader-Willi syndrome	Roux-en-Y gastric bypass
Miyata et al.[14]	Case report	1	4	Prader-Willi syndrome	Vertical banded gastroplasty
Brossy[15]	Case report	1	4	Prader-Willi syndrome	Biliopancreatic diversion
Anderson et al.[16]	Case series	11	4	Prader-Willi syndrome	10 – Roux-en-Y gastric bypass 1 – Gastric banding
Laurent-Jaccard et al.[17]	Case series	3	4	Prader-Willi syndrome	Biliopancreatic diversion
Marinari et al.[18]	Case series	15	4	Prader-Willi syndrome	Biliopancreatic diversion
Gibbons et al.[19]	Scoping review	49	3a	48 – Prader-Willi syndrome 1 – unknown	24 – Biliopancreatic diversion 12 – Roux-en-Y gastric bypass 5 – others

N = number of individuals.

into consideration in the decision-making process regarding which technique to use. Historically, predominantly restrictive procedures such as sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) and gastric banding were avoided among individuals whose intellectual deficit was more severe, such as in cases of Prader-Willi syndrome.[16-18] However, this trend diminished over the years, to the point that nowadays Roux-en-Y and mini-gastric bypasses, and even sleeve gastrectomy, in which weight loss relies exclusively on a restrictive mechanism, are considered valid options.[8-15,19] There is newer evidence showing that restrictive techniques may be safe and effective in this group of subjects.[6,9,11] In individuals whose deficit is slight or even borderline, predominantly restrictive procedures do not present any formal contraindications.[6,7,20-22] With the sole exception of the study by Miyata et al.,[14] in which an individual with Prader-Willi syndrome presented an initial improvement of metabolic and weight conditions, followed by progressive worsening, the vast majority of the studies have consistently observed significant improvements following a variety of techniques, regarding both metabolic features and weight loss, albeit to a lesser extent than what is observed in the general population with obesity when bariatric surgery is implemented.[6-13,15-19]

More studies are necessary, in order to provide evidence of higher quality that could lead to possible algorithms for this heterogeneous group of individuals. There is recent evidence that even mild cognitive impairment may play a role in the outcomes from bariatric surgery, such that it may lead to worse results and, especially, poor adherence to long-term follow-up.[23,24] Nonetheless, a recent study by Rochette et al.[25] observed a significant decrease in the prevalence of mild cognitive impairment after bariatric surgery. Whether this may be applicable to individuals with severe cognitive disability remains to be further investigated.

CONCLUSION

Bariatric surgery is feasible and safe among cognitively impaired individuals, but further research is necessary.

REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization ; 2014.
2. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753-61.
3. Melville CA, Cooper SA, McGrother CW, Thorp CF, Collacott R. Obesity in adults with Down syndrome: a case-control study. J Intellect Disabil Res. 2005;49(Pt 2):125-33.
4. Rimmer JH, Braddock D, Fujiura G. Prevalence of obesity in adults with mental retardation: implications for health promotion and disease prevention. Ment Retard. 1993;31(2):105-10.
5. Ohyama Y, Utsugi T, Uchiyama T, et al. Prevalence of diabetes in adult patients with Down's syndrome living in a residential home. Diabetes Care. 2000;23(5):705-6.
6. Heinberg LJ, Schauer PR. Intellectual disability and bariatric surgery: a case study on optimization and outcome. Surg Obes Relat Dis. 2014;10(6):e105-8.
7. Daigle CR, Schauer PR, Heinberg LJ. Bariatric surgery in the cognitively impaired. Surg Obes Relat Dis. 2015;11(3):711-4.
8. Bauchowitz AU, Gonder-Frederick LA, Olbrisch ME, et al. Psychosocial evaluation of bariatric surgery candidates: a survey of present practices. Psychosom Med. 2005;67(5):825-32.
9. Alqahtani AR, Elahmedi MO, Al Qahtani AR, Lee J, Butler MG. Laparoscopic sleeve gastrectomy in children and adolescents with Prader-Willi syndrome: a matched-control study. Surg Obes Relat Dis. 2016;12(1):100-10.
10. Musella M, Milone M, Leongito M, et al. The mini-gastric bypass in the management of morbid obesity in Prader-Willi syndrome: a viable option? J Invest Surg. 2014;27(2):102-5.
11. Fong AK, Wong SK, Lam CC, Ng EK. Ghrelin level and weight loss after laparoscopic sleeve gastrectomy and gastric mini-bypass for Prader-Willi syndrome in Chinese. Obes Surg. 2012;22(11):1742-5.
12. Kobayashi J, Kodama M, Yamazaki K, et al. Gastric bypass in a Japanese man with Prader-Willi syndrome and morbid obesity. Obes Surg. 2003;13(5):803-5.
13. Braghetto Miranda I, Rodríguez NA, Debandi Lizárraga A, et al. Síndrome Prader Willi asociado a obesidad mórbida: tratamiento quirúrgico [Surgical treatment of morbid obesity associated to Prader-Willi syndrome: report of 1 case]. Rev Med Chil. 2003;131(4):427-31.
14. Miyata M, Dousei T, Harada T, et al. Metabolic changes following gastroplasty in Prader-Willi syndrome--a case report. Jpn J Surg. 1990;20(3):359-64.
15. Brossy JJ. Biliopancreatic bypass in the Prader-Willi syndrome. Br J Surg. 1989;76(3):313.
16. Anderson AE, Soper RT, Scott DH. Gastric bypass for morbid obesity in children and adolescents. J Pediatr Surg. 1980;15(6):876-81.
17. Laurent-Jaccard A, Hofstetter JR, Saegesser F, Chapuis Germain G. Long-term Results of treatment of Prader-Willi Syndrome by Scopinaro's Bilio-pancreatic Diversion. Study of Three cases and the Effect of Dextrofenfluramine on the Postoperative Evolution. Obes Surg. 1991;1(1):83-7.
18. Marinari GM, Camerini G, Novelli GB, et al. Outcome of biliopancreatic diversion in subjects with Prader-Willi Syndrome. Obes Surg. 2001;11(4):491-5.
19. Gibbons E, Casey AF, Brewster KZ. Bariatric surgery and intellectual disability: Furthering evidence-based practice. Disabil Health J. 2017;10(1):3-10.
20. Foerste T, Sabin M, Reid S, Reddihough D. Understanding the causes of obesity in children with trisomy 21: hyperphagia vs physical inactivity. J Intellect Disabil Res. 2016;60(9):856-64.
21. Michalik M, Frask A, Lech P, Zdrojewski M, Doboszynska A. The usefulness of biliopancreatic diversion/Scopinaro operation in treatment of patients with Prader-Willi syndrome. Wideochir Inne Tech Maloinwazyjne. 2015;10(2):324-7.

22. Bingham NC, Rose SR, Inge TH. Bariatric surgery in hypothalamic obesity. Front Endocrinol (Lausanne). 2012;3:23.
23. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring). 2013;21 Suppl 1:S1-27.
24. Galioto R, Gunstad J, Heinberg LJ, Spitznagel MB. Adherence and weight loss outcomes in bariatric surgery: does cognitive function play a role? Obes Surg. 2013;23(10):1703-10.
25. Rochette AD, Spitznagel MB, Strain G, et al. Mild cognitive impairment is prevalent in persons with severe obesity. Obesity (Silver Spring). 2016;24(7):1427-9.

Conflict of interest: None
Sources of interest: None

Date of first submission: October 25, 2016
Last received: November 14, 2016
Accepted: December 7, 2016

Address for correspondence:
Everton Cazzo
Departamento de Cirurgia, Faculdade de Ciências Médicas da
Universidade Estadual de Campinas (FCM-Unicamp)
Rua Alexander Fleming, s/nº
Campinas (SP) — Brasil
CEP 13085-000
Tel. (+55 19) 3521-7405
E-mail: notrevezzo@yahoo.com.br

Report of a rare case and review of adult intestinal duplication at the opposite side of mesenteric margin

Zhi-Hao Huang[I], Zi-Hao Wan[II], Vikash Vikash[III], Sindhu Vikash[IV], Cong-Qing Jiang[V]

Department of Colorectal and Anal Surgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China

[I]MD, MSc. Surgeon, Department of Colorectal and Anal Surgery, Wuhan University Zhongnan Hospital, Wuhan, Hubei Province, China.

[II]MD, MSc. Surgeon, Department of Orthopedic Surgery, Wuhan University Zhongnan Hospital, Wuhan, Hubei Province, China.

[III]MD, PhD. Physician, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China.

[IV]MD, PhD. Physician, Department of Medicine, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, Sindh, Pakistan.

[V]MD, PhD. Surgeon, Department of Colorectal and Anal Surgery, Wuhan University Zhongnan Hospital, Wuhan, Hubei Province, China.
orcid.org/0000-0002-5063-6299

KEY WORDS:
Adult.
Intestines.
Congenital abnormalities.

ABSTRACT

CONTEXT: To study the previously discovered clinical entity of adult intestinal duplication and its treatment, and propose an extension to its existing classification.

CASE REPORT: We report the case of an adult male with abdominal pain, constipation and vomiting. This patient underwent surgical separation of adhesions, reduction of torsion and intestinal decompression. Postoperative pathological findings confirmed the rare diagnosis of intestinal duplication.

CONCLUSION: Adult intestinal duplication is quite rare. Its clinical manifestations are nonspecific. From this finding of intestinal duplication originating at the opposite side of the mesenteric margin, a further extension of the existing anatomical classification is proposed.

INTRODUCTION

Digestive tract duplication is a rare congenital malformation that can involve any segment of the gastrointestinal tract.[1] It is common during the fetal, neonatal and pediatric period. Clinicians are prone to misdiagnose it because of the nonspecific clinical signs. Although the diagnostic significance of enteroscopic and radionuclide imaging has been reported, there are limitations to these imaging techniques because of the diverse symptoms and complexity of anatomical sites of this disease. At present, surgical resection is still the main treatment. The results from a systematic search of the literature in the main database is shown in **Table 1**. We aimed to compare and contrast our patient's clinical data and associated previous studies, in order to further discuss the diagnosis and treatment options.

CASE REPORT

A 53-year-old male patient presented to our emergency department with the main complaint of abdominal pain and constipation for two days. His past medical and family histories were unremarkable. He had been smoking for 20 years (10-15 cigarettes a day). He denied having any allergies or previous illicit drug or alcohol use.

On physical examination, the patient's body temperature was 36.8 °C, the abdomen was soft and slightly bulged, there were no apparent bowel movements, no apparent mass on palpation, negative shifting dullness, no auscultated sounds of an overactive bowel and a digital rectal examination was negative for any mass or blood. Laboratory tests suggested slight elevation in white blood cell count. An abdominal radiograph revealed multiple air-fluid levels in the intestinal gut (**Figure 1**). Abdominal ultrasonography showed a dilated bowel sharing a common continuous wall with the distal segment (**Figure 2**). Computed tomography (CT) revealed thickening of the small intestinal wall and cystic intestinal dilation proximal to stenosis with clear margins (**Figure 3**).

The patient was given symptomatic treatment consisting of antibiotics, antacids, antispasmodics and enema. After one day, he presented with noticeable abdominal swelling with unbearable abdominal pain, total abdominal tenderness, rebound tenderness and bowel sounds that had decreased in intensity.

Subsequently, exploratory laparotomy was performed. On surgical exploration, around 100 ml of transparent ascites fluid and torsion of a dilated small bowel loop with surrounding edema were noticed. Moreover, a large cystic mass was detected hanging from the wall of the small intestine

Figure 1. Abdominal radiograph: multiple gas-liquid planes in the intestinal gut.

into the pelvic cavity, which had led to formation of inflammatory adhesions with adnexa. The adhesions were then bluntly separated, and the mass was found to be located at around 150 cm distally to the Treitz ligament. The mass was ischemic, dark in color, and covered with pus. The basal wall of the mass was weaker than the healthy loops around it, and the basal diameter was around 4.5 cm. After relieving the twisted mass and the surrounding small intestine, we noticed inflammatory edema, and dilation of the proximal intestinal wall. Several adhesive masses with punctate ischemia and inflammation, 20 cm proximally to the lesion, was also noted (**Figure 4**).

We decided to loop-out the jejunum approximately 35 cm proximally and 5 cm distally to the base of the mass. After resection of about 40 cm of bowel, which included the mass and the ischemic small intestine, the remaining bowel segments were anastomosed using a stapler. An intraoperative diagnosis of intestinal duplication, obstruction and torsion of the small intestine was made. The pathological findings are shown in **Figure 5**.

Postoperatively, the patient was kept under parenteral nutrition. He recovered well and began eating nine days after the surgery. He was discharged fifteen days after the surgery, and no sign of recurrence was observed after three months of follow-up.

Table 1. Summary of adult patients with small intestinal duplications as found in the United States National Institutes of Health's National Library of Medicine (PubMed) database as of July 20, 2017

Database	Search strategies				Papers found	Related papers
MEDLINE (via PubMed)	((("Adult"[Mesh]) AND "Intestine, Small"[Mesh]) AND "Congenital Abnormalities"[Mesh]) AND duplication[Title/Abstract]				40	20
Study (year)	**Age (years)/gender**	**Presenting features**	**Surgical treatment**	**Form**	**Size (cm)**	**Malignancy**
Ho (2012)[3]	25/male	Abdominal pain	Yes	Tubular	NR	No
Vivier et al. (2013)[4]	32/female	Routine control examination	Yes	Cystic	2	No
Handra-Luca et al. (2013)[5]	65/male	Routine control examination	Yes	Tubular	8	Yes
Barbosa et al. (2015)[6]	36/male	Abdominal pain, vomiting	Yes	Cystic	NR	No
Yu et al. (2014)[7]	24/female	Abdominal pain	Yes	Cystic	28 × 20	No
Li et al. (2013)[8]	25/male	Abdominal pain, weight loss	Yes	Tubular	15.5 × 4	No
Nussbaum et al. (2014)[9]	51/male	Abdominal pain, bloody stools	Yes	Tubular	9.5 × 2	Yes
Kim et al. (2014)[10]	19/female	Abdominal pain	Yes	Cystic	2,5	No
Park et al. (2014)[11]	36/female	Abdominal pain	Yes	Cystic	12	No
Martínez-Alcala et al. (2014)[12]	37/female	Abdominal pain, vomiting	Yes	Cystic	5	No
Furuya et al. (2012)[13]	70/female	Abdominal pain	Yes	Cystic	3	Yes
Miloudi et al. (2012)[14]	26/male	Abdominal pain, vomiting	Yes	Cystic	4	No
Palacios et al. (2013)[15]	35/female	Routine control examination	Yes	Cystic	1.3	No
Antaki et al. (2013)[16]	21/male	Abdominal pain	Yes	Cystic	NR	No
Kusnierz et al. (2014)[17]	31/female	Abdominal pain, nausea, lack of appetite	Yes	Cystic	2.9 × 2.6	No
Cheng et al. (2014)[18]	49/male	Gastrointestinal bleeding, melena passage	Yes	Cystic	NR	No
Kurien et al. (2014)[19]	NR/female	Abdominal pain	Yes	Cystic	NR	No
Kachi et al. (2016)[20]	64/female	Abdominal pain	Yes	Cystic	4	No
Gupta et al. (2016)[21]	20/male	Constipation, vomiting	Yes	Cystic	NR	No
Inoue et al. (2016)[22]	56/male	Appetite loss, palpitations, orthostatic syncope, hematochezia	Yes	Cystic	NR	No

NR = not reported.

DISCUSSION

Digestive tract duplication is more common in men and tends to occur most frequently in the small intestine. It characteristically arises from the mesenteric border of the bowel.[2] Although several cases (**Table 1**)[3-22] of adult intestinal duplication have been reported, the present case was unique, in that the mass emerged from the opposite side of the mesenteric margin, which made intestinal obstruction and torsion more likely to occur.

The broadly accepted classification of intestinal duplication consists of five types: intestinal membrane type, intestinal wall cyst type, extra-intestinal cyst type, extra-intestinal tubular type

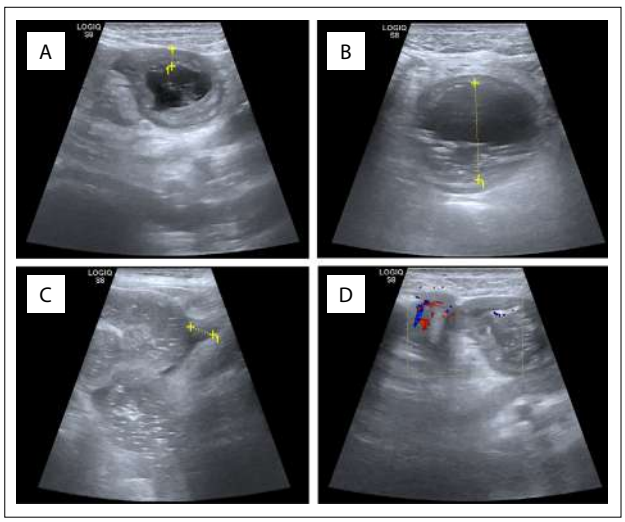


Figure 2. Abdominal ultrasonography: (A) A distended bowel can be seen below the umbilicus, and peristalsis is not apparent. The wall of the tube is thickened, and the lumen at the beginning of its expansion is compressed. (B) A dark area is seen between the intestines. (C) The intestinal wall is raised into the lumen, and the two intestinal tubes share the same wall of the bowel canal. (D) A small amount of colored blood flow signal can be seen on the wall of the dilated intestinal tube.

Figure 3. Abdominal and pelvic computed tomography examination: A large cystic mass with a clear boundary can be seen.

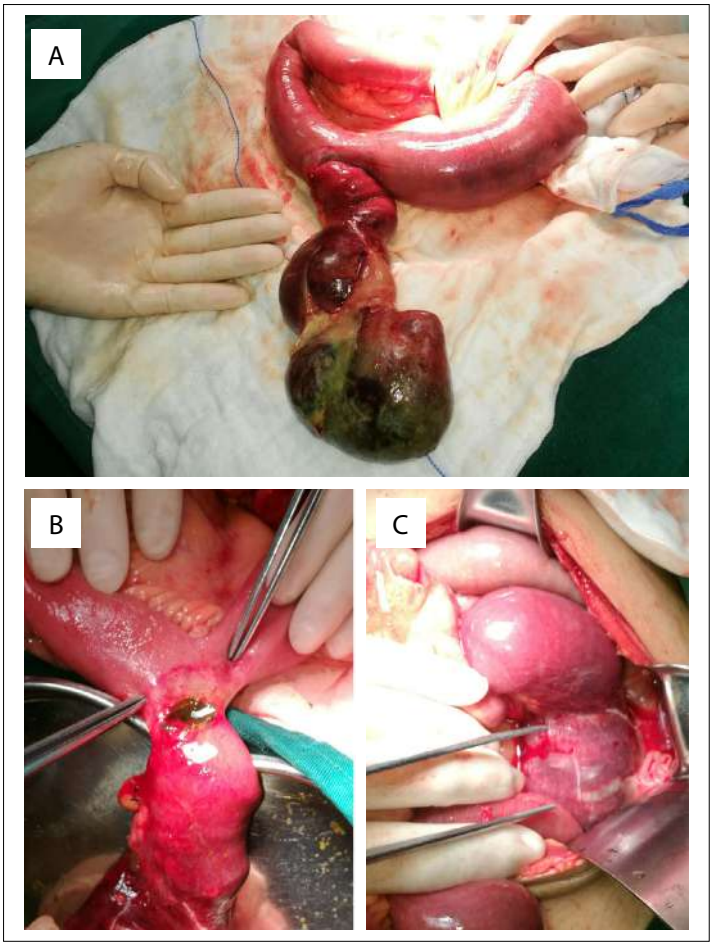


Figure 4. Intraoperative findings (gross specimens): (A) The mass was generally ischemic, with darker color; the surface was covered with pus and no perforation was found; the proximal segment of the small intestine was dilated and hypertrophic, with inflammatory edema and punctate ischemia. (B) The basement wall was relatively weak, and the border of the normal bowel was clear. (C) Twisted sticky joints at the base of the mass compressed the adjacent normal intestinal canal.

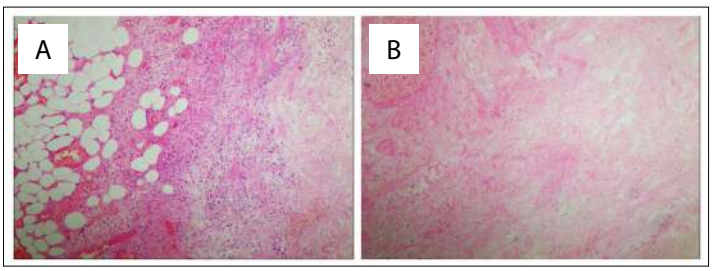


Figure 5. Pathological findings: (A) Small bowel cystic lesions: hemorrhage and necrosis were observed in the intestinal wall, and mesenteric vascular dilatation and congestion were observed, which was consistent with bleeding and necrotic alterations in the volvulus (hematoxylin and eosin staining, magnification x 100). (B) Intestinal ischemia and inflammatory tissue: examination of intestinal wall tissue showed presence of a mucosal layer of chronic inflammatory cell infiltration, with submucosal edema and thickening, while the smooth muscle layer was not abnormal (hematoxylin and eosin staining, magnification x 100).

and solitary type.[23] The prevalence of gastrointestinal duplication varies, but it is more common in the ileum and ileocolic segment. Intestinal duplication is usually cystic or tubular in nature and often continuous with the regular bowel wall, and it shares the muscle and mucosal layer.[24]

We hypothesized that the course of this case would have begun with repeated duplication of the jejunum, thus resulting in repeated intestinal edema, enlargement and inflammatory changes. Subsequently, under gravitational traction, the inflamed bowel would have been able to twist easily. Abnormal duplication would then have occurred and the adjacent bowel walls would have aligned and compressed each other.

The clinical presentation of intestinal duplication depends on the structure, size and site of the lesion in relation to the surrounding structures. Because of nonspecific signs and symptoms, it is often misdiagnosed as cases of other causes of an acute abdomen at the acute stage, or is labeled as Meckel's diverticulum at the chronic or asymptomatic stages. Meckel's diverticulum has a separate blood supply, while intestinal duplication shares a blood supply with the surrounding intestinal tract. Moreover, intestinal duplication is characterized by well-developed smooth muscle, which is absent from intestinal diverticula.

At present, the types of imaging that are suggested are ultrasonography, gastrointestinal radiography, computed tomography, radionuclide imaging and magnetic resonance imaging.[25,26] Over recent years, comparatively more cases have been diagnosed during the fetal period, and this has been attributed to widespread use of obstetric ultrasound scanning. Ultrasonography reveals a separate echo structure, double wall sign and a shared bowel wall, which points towards the potential abnormality. Therefore, ultrasonography is preferred over other types of imaging. It has also been reported that ^{99m}Tc radionuclide imaging has diagnostic value for cases of suspected gastric mucosal ectopy.[27] However, in our case, no gastric mucosal ectopy was seen in the sectioned specimen.

In this disease, surgical treatment is the preferred option. The choice of surgical procedures depends on multiple factors, such as the location, type and relationship with the surrounding tissue.

CONCLUSION

The classification of digestive tract duplication is diverse. This is the first case report on small intestinal duplication on the opposite side of the mesenteric margin. It potentially extends the anatomical classification of intestinal duplication.

REFERENCES

1. Blank G, Konigsrainer A, Sipos B, Ladurner R. Adenocarcinoma arising in a cystic duplication of the small bowel: case report and review of literature. World J Surg Oncol. 2012;10:55.
2. Keramidas DC, Demetriades DM. Total tubular duplication of the colon and distal ileum combined with transmesenteric hernia: surgical management and long-term-results. Eur J Pediatr Surg. 1996;6(4):243-4.
3. Ho YC. Total colorectal and terminal ileal duplication presenting as intussusception and intestinal obstruction. World J Gastroenterol. 2012;18(43):6338-40.
4. Vivier PH, Beurdeley M, Bachy B, Aguilella C, Ickowicz V, Lemoine F, et al. Ileal duplication. Diagn Interv Imaging. 2013;94(1):98-100.
5. Handra-Luca A. Adult ileal duplication revealed by a colon adenoma. Surg Today. 2013;43(11):1335-6.
6. Barbosa L, Soares C, Povoa AA, Maciel JP. Ileal duplication: an unusual cause of intestinal obstruction in adult life. BMJ Case Rep. 2015;2015.
7. Yu Y, Wu JS, Ke ZW. Giant chylous cyst and ileal duplication in a young adult. Singapore Med J. 2014;55(5):e77-81.
8. Li BL, Huang X, Zheng CJ, Zhou JL, Zhao YP. Ileal duplication mimicking intestinal intussusception: a congenital condition rarely reported in adult. World J Gastroenterol. 2013;19(38):6500-4.
9. Nussbaum DP, Bhattacharya SD, Jiang X, Cardona DM, Strickler JH, Blazer DG, 3rd. Gastroesophageal heterotopia and HER2/neu overexpression in an adenocarcinoma arising from a small bowel duplication. Arch Pathol Lab Med. 2014;138(3):428-31.
10. Kim HS, Sung JY, Park WS, Kim YW. An ileal duplication cyst manifested as an ileocolic intussusception in an adult. Turk J Gastroenterol. 2014;25 Suppl 1:196-8.
11. Park JY, Her KH, Kim BS, Maeng YH. A completely isolated intestinal duplication cyst mimicking ovarian cyst torsion in an adult. World J Gastroenterol. 2014;20(2):603-6.
12. Martinez-Alcala Garcia F, Perez Pozo JM, Martinez-Alcala Garcia A, Ciria Avila JA, Martinez Alcala F. [Duodenal duplication cyst and its endoscopic resolution]. Gastroenterol Hepatol. 2014;37(4):274-5.
13. Furuya K, Hada M, Sugai H, Miyasaka Y, Nakagomi H, Oyama T, et al. Gastrointestinal stromal tumor arising in an ileal duplication: report of a case. Surg Today. 2012;42(12):1234-9.
14. Miloudi N, Mzoughi Z, Ben Abid S, Sabbagh S, Arfa N, Khalfallah MT. [Duodenal duplication treated surgically]. La Tunisie medicale. 2012;90(11):837-8.
15. Palacios A, De Vera M, Martinez-Escoriza JC. Prenatal sonographic findings of duodenal duplication: case report. J Clin Ultrasound. 2013;41 Suppl 1:1-5.
16. Antaki N, Abboud D, Lemmers A, Antaki F, Deviere J. Acute recurrent pancreatitis secondary to the rare association of a duodenal duplication cyst and a pancreas divisum. Clin Res Hepatol Gastroenterol. 2013;37(1):e32-6.
17. Kusnierz K, Pilch-Kowalczyk J, Gruszczynska K, Baron J, Lucyga M, Lampe P. A duodenal duplication cyst manifested by duodenojejunal intussusception and chronic pancreatitis. Surgery. 2014;156(3):742-4.
18. Cheng CL, Liu NJ, Yu MC. Intraluminal tubular duodenal duplication with bleeding. Clin Gastroenterol Hepatol. 2014;12(2):e10-1.

19. Kurien RT, Chowdhury SD, Unnikrishnan LS, Simon EG, Dutta AK, Mahanta K, et al. Endoscopic treatment of a duodenal duplication cyst. Endoscopy. 2014;46 Suppl 1 UCTN:E583-4.
20. Kachi A, Haddad F, Geagea A, Tohmeh MJ. Unusual case of jejunal duplication in a 64-year-old female. J Med Liban. 2016;64(1):50-3.
21. Gupta A, Chakaravarthi K, Pattnaik B, Kaman L. Duplication cyst of ileum presenting as acute intestinal obstruction in an adult. BMJ Case Rep. 2016;2016.
22. Inoue K, Sakiyama T, Setoyama K, Iwashita Y, Saito S, Hanada N, et al. [Jejunal duplication in an adult presenting with hematochezia]. Nihon Shokakibyo Gakkai Zasshi. 2016;113(4):662-71.
23. Fuyou H, Hong Y, Yan S. The diagnosis and classification of intestinal duplication. Chinese Journal of Pediatric Surgery. 1997;18(2):91-3. Available from: http://eng.med.wanfangdata.com.cn/PaperDetail.aspx?qkid=xrwk&qcode=xrwk199702010#. Accessed in 2017 (Sep 6).
24. Sinha A, Ojha S, Sarin YK. Completely isolated, noncontiguous duplication cyst. Eur J Pediatr Surg. 2006;16(2):127-9.
25. Nadatani Y, Watanabe T, Sugawa T, Eguchi S, Shimada S, Otani K, et al. Double-balloon endoscopy WAS effective in diagnosing small intestinal duplication: a case report. SpringerPlus. 2016;5(1):1598.
26. Ogino H, Ochiai T, Nakamura N, Yoshimura D, Kabemura T, Kusumoto T, et al. Duplication cyst of the small intestine found by double-balloon endoscopy: a case report. World J Gastroenterol. 2008;14(24):3924-6.
27. Schwesinger WH, Croom RD, 3rd, Habibian MR. Diagnosis of an enteric duplication with pertechnetate 99mTc scanning. Ann Surg. 1975;181(4):428-30.

Conflict of interest: None
Sources of funding: None

Date of first submission: June 15, 2017
Last received: July 27, 2017
Accepted: August 3, 2017

Address for correspondence:
Cong-Qing Jiang
Department of Colorectal and Anal Surgery, Zhongnan Hospital of Wuhan University
169 Donghu Road
Wuhan — Hubei Province 430071 — China
Tel. + 86-027-67812960
E-mail: wb002554@whu.edu.cn

DOI: 10.1590/1516-3180.2017.0104210417

Wealth inequality and weak primary care in the city of São Paulo: ingredients for a dysfunctional and ineffective healthcare system

Rodrigo Diaz Olmos[I]

Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo (SP), Brazil

[I]Professor, Department of Internal Medicine, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo (SP), Brazil.

I read the Editorial[1] with interest and agree that preventive interventions should be directed towards social determinants instead of spending huge amounts of healthcare resources on biomedical interventions that may produce more harm than benefit. As the editor pointed out, actions to improve health are mainly outside of the Health Department. Therefore, I too urge the new mayor, Mr. Doria, to adopt science-driven actions to improve health in São Paulo.

I would like to include some ideas that add to the proposal made by the Journal's Editor. Apart from the factors mentioned in the editorial, there are some other social determinants that significantly affect health outcomes, such as household income, education, wealth inequality and leisure, working and environmental conditions. These, in turn, affect downstream factors, particularly lifestyle choices.[2] All of these play a more important role in improving health than does medical care. Addressing social determinants of health is an important step towards reaching a healthier society. Social injustice makes people ill and, thus, reduction of these inequities is an ethical imperative.

Medical care is also a determinant of health. However, its importance depends on how it is organized. Medical care based on specialty care, without the coordinating and gatekeeper roles of primary care, tends to be costly, inequitable, medicalizing and worse overall. On the other hand, healthcare based on accessible, continuous, person-centered and integrated primary care tends to produce better health outcomes at less cost.

Adequate investments in the primary healthcare workforce are mandatory, and this means maximizing workforce capacity and stimulating teaching in primary care units. Including teaching within community services as a priority would be cost-effective, since primary care residents trained in this setting would immediately increase the capacity of these services and ultimately expand the primary care workforce.[3] Investments in high-tech imaging facilities, particularly in the private healthcare sector, on the other hand, are not cost-effective and may produce more harm than good.

Another idea for improving community healthcare services is to change the way in which access is provided within primary care units. Traditionally, scheduling has been based on a variety of appointment types (diabetic care, prenatal care, women's health, etc.), with a backlog of months and chaotic procedures for triaging patients into crowded office schedules. It produces awkward accessibility to primary care and leads to low patient satisfaction, high emergency department use and overall ineffective primary care. I propose the Advanced Access model, which has increasingly been shown to reduce waiting times within primary care. However, although its principles are potent, they are counter to deeply held beliefs and established practices.[4] Thus, adopting this model requires leadership and political support.

The last suggestion is to redistribute daily general practice activities from physicians to other healthcare professionals, particularly nurses and pharmacists. This offers a potential solution for primary care supply and demand, thereby empowering other healthcare providers and increasing

their satisfaction and effectiveness. Although Brazil seems to stick to old-fashioned, early-20th century practices, there is good recent international evidence for task-shifting of activities from physicians to nurses.[5]

Please, Mr. Doria, read this carefully.

REFERENCES

1. Lotufo PA. Green areas, clean air and cardiovascular health in the city of São Paulo. Sao Paulo Med J. 2017;135(1):1-3.
2. Braveman P, Egerter S, Williams DR. The social determinants of health: coming of age. Annu Rev Public Health. 2011;32:381-98.
3. Rieselbach RE, Crouse BJ, Frohna JG. Teaching primary care in community health centers: addressing the workforce crisis for the underserved. Ann Intern Med. 2010;152(2):118-22.
4. Murray M, Berwick DM. Advanced access: reducing waiting and delays in primary care. JAMA. 2003;289(8):1035-40.
5. Maier CB, Aiken LH. Task shifting from physicians to nurses in primary care in 39 countries: a cross-country comparative study. Eur J Public Health. 2016;26(6):927-34.

Conflict of interest: None
Sources of funding: None

Date of first submission: April 9, 2017
Last received: April 9, 2017
Accepted: April 21, 2017

Address for correspondence:
Rodrigo Diaz Olmos
Departamento de Clínica Médica, Faculdade de Medicina da
Universidade de São Paulo (FMUSP)
Av. Prof. Lineu Prestes, 2.565
São Paulo (SP) — Brasil
CEP 05508-000
Tel. (+55 11) 3091-9433
E-mail: olmos.rodrigo@gmail.com

DOI: 10.1590/1516-3180.2017.0122210517

Unethical research trend: shadow libraries

Zeeshan Asim[I], Shahryar Sorooshian[II]

School of Industrial Management, Universiti Malaysia Pahang, Kuantan, Malaysia

[I]Doctoral Student, School of Industrial Management, Universiti Malaysia Pahang, Kuantan, Malaysia.

[II]Medical doctor and Senior Lecturer, School of Industrial Management, Universiti Malaysia Pahang, Kuantan, Malaysia

Dear Editor

Research articles spread knowledge that has been shaped by scientific communities. Access to this literature is essential for any scholar. Evidently,"biblio gifts" are easily accessible online without any charge from text-sharing platforms. Similarly, virtual groups in social networking websites such as Facebook, LinkedIn, Twitter and virtual blogs are used as pirated platforms. However little argument has been acknowledged regarding such platforms, especially concerning the size of the digital database, the major research areas covered and where these research articles come from (primary sources).

Complete possession of intellectual property for a large proportion of the scholarly database has been seized by a number of publishers. Many research articles are barricaded behind paywalls and remain unavailable for research scholars. In recent times, there has been an enormous expansion of open-access journals (OAJs). In 2009 alone, around 4,800 OAJs published approximately 190,000 research articles. However, despite expansion of this number to over 10,000 OAJs in 2015,[1] Fuchs and Sandoval revealed that 88% of all the existing journals were still blocked and only 12% could truly be categorized as OAJs.[2] Consequently, some readers have become encouraged to use pirate web platforms such as Sci-Hub and Library Genesis (LibGen), which enable free access to paid content such as journal databases and digital libraries, in order to access paid research content. Such malpractices can alternatively be regarded either as unethical and a criminal offense or as an act of civil disobedience.[3]

While piracy has eventually become an inevitable subject for debate within the domain of scholarly communications, the public experience of the Sci-Hub and LibGen platforms has stimulated the decade-old debate about the potential contribution of the commercial aspects of scholarly publishers, digital libraries and copyright towards creating an atmosphere within which the outcome of scholarly enquiry is uniformly accessible for all.

Sci-Hub and LibGen became known as infringing web platforms that allowed unauthorized pirated research content from copyright scholarly databases to be accessible. Their initial aim was to assist researchers who were unable to have institutional access to these digital libraries and were reluctant to pay the subscription fees per research article. These unauthorized web platforms, which can be considered to be shadow libraries, offer property and contravene access for academic purposes.[4] High attention was drawn to them after a Kazakh computer programmer, Alexandra Elbakyan, who was recognized as the owner of Sci-Hub, faced enormous public criticism through a lawsuit filed by Elsevier against the unauthorized web platform and the programmer herself in a New York court (Elsevier Inc. et al. versus Sci-Hub et al. Case No. 1:15-cv-04282-RWS).[5]

To conclude, pirated web platforms like Sci-Hub and LibGen, along with some access support groups in social networking websites, e.g. Facebook, Twitter and all the virtual blogs, are considered by many traditional publishers to be a major threat. Many researchers find it irresistible to choose a simple interface in order to access a wide range of research articles. However, this is not a justification for using infringing web platforms, especially when morals within publication are a subject of deep concern from an ethical viewpoint.

REFERENCES

1. Björk BC. A study of innovative features in scholarly open access journals. J Med Internet Res. 2011;13(4):e115.
2. Fuchs C, Sandoval M. The Diamond Model of Open Access Publishing: Why Policy Makers, Scholars, Universities, Libraries, Labour Unions and the Publishing World Need to Take Non-Commercial, Non-Profit Open Access Serious. triple. 2013;13(2):428-43. Available from: http://triplec.at/index.php/tripleC/article/view/502/497. Accessed in 2017 (Jul 21).
3. Sample I. Harvard University says it can't afford journal publishers' prices. The Guardian; 2012. Available from: https://www.theguardian.com/science/2012/apr/24/harvard-university-journal-publishers-prices. Accessed in 2017 (Jun 2).
4. Bodó B. Pirates in the Library - An Inquiry into the Guerilla Open Access Movement. Paper prepared for the 8th Annual Workshop of the International Society for the History and Theory of Intellectual Property, CREATe, University of Glasgow, UK, July 6-8, 2016. Available from: https://ssrn.com/abstract=2816925. Accessed in 2017 (Jun 2).
5. Tran D. Elsevier V. Sci-hub: Piracy of knowledge and the jurisdictional reach of U.S. Copyright law. Wake Forest Journal of Business and Intellectual Property Law, 2017;17(2):201-23. Available from: https://litigation-essentials.lexisnexis.com/webcd/app?action=DocumentDisplay&crawlid=1&doctype=cite&docid=17+Wake+Forest+J.+Bus.+%26+Intell.+Prop.+L.+198&srctype=smi&srcid=3B15&key=81adbf330dce5251baeba480de297ca9. Accessed in 2017 (Jun 2).

Conflict of interest: None
Sources of funding: None

Date of first submission: April 26, 2017
Last received: May 18, 2017
Accepted: May 22, 2017

Address for correspondence:
Zeeshan Asim
School of Industrial Management, Universiti Malaysia Pahang,
Lebuhraya Tun Razak, 26300 Gambang, Kuantan, Pahang Darul Makmur
Tel. +0601121620892
Kuantan — Malaysia
E-mail: zeeshanasimump@gmail.com

DOI: 10.1590/1516-3180.2017.0277100917erratum

In the manuscript "Strategies to optimize MEDLINE and EMBASE search strategies for anesthesiology systematic reviews. An experimental study", published in the Sao Paulo Med J. 2018 Jan 15:0. doi: 10.1590/1516-3180.2017.0277100917. [Epub ahead of print]:

Where it read:
"Volpato ESN, Betini M, Puga ME, Agarwal A, Cataneo AJM, Oliveira LD, Bazan R, Braz LG, Pereira JEG8, Dib RE"

It should read:
"Volpato ESN, Betini M, Puga ME, Agarwal A, Cataneo AJM, Oliveira LD, Bazan R, Braz LG, Pereira JEG8, El Dib R"

AIM AND EDITORIAL POLICY

Indexing and scope

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is now published bimonthly by the Associação Paulista de Medicina. It accepts articles in the fields of clinical health science (internal medicine, gynecology & obstetrics, mental health, surgery, pediatrics, epidemiology and public health). Articles will be accepted in the form of original articles, narrative reviews, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

The journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the Editorial Team, who will check whether the text complies with the journal's Instructions for Authors. The Journal has adopted the CrossRef Similarity Check system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be rejected.

When the format of the manuscript is deemed acceptable, the Editorial Team will submit the article to the Editor-in-Chief who will assign at least two reviewers/referees with expertise in the theme, to assess it. The authors will then receive the reviewers' evaluation and will be required to provide all further information requested and the corrections that may be necessary. Changes to the text should be highlighted, accompanied by a letter answering the referees' comments, point by point.

Once the Editorial Team has received the revised manuscript, the text will be sent to the Editor-in-Chief for a decision. Manuscripts that are suitable for publication according to their scientific merit will be considered "accepted." However, all of them will subsequently be scrutinized to check for any problems regarding sentence construction, spelling, grammar, bibliographical references and other matters that may arise. The authors should contribute towards improving the manuscript by making it as readable as possible. Lastly, the Editorial Team will provide page proofs for the authors to approve. No article is published without this final procedure.

São Paulo Medical Journal does not charge authors for publication: there are no submission fees for the evaluation of articles. The Journal is an open-access publication that does not charge the readers, either. Articles accepted for publication become the journal's property for copyright purposes, in accordance with the Creative Commons attribution-type BY.

THE MANUSCRIPT AND TYPES OF ARTICLES

General guidelines: for all types of articles

All manuscripts must be submitted in English with a covering letter signed by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text has not been nor will be submitted for publication in any other journal.
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest.
3. a statement that implementation of the study was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles).
4. a brief description of contributorship.
5. a list of a minimum of five potential referees outside of the authors' institutions.

The Journal recommends that all articles submitted must comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (available at www.icmje.org).[1] This means that each type of study must be described in accordance with the specific quality guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9]

Abbreviations must not be used, even those in everyday use. Drugs or medications must be referred to using their generic names, avoiding casual mention of commercial or brand names. All drugs should be followed by the dosage and posology used. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses.

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing the study. The Journal supports the position taken by the International Committee of Medical Journal Editors (http://www.icmje.org) regarding authorship. This body's recommendations should be read to obtain clarifications regarding the criteria for authorship.

For any manuscript, all statements in the text that do not result from the study presented for publication in the São Paulo Medical Journal but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data is only available electronically.

Articles must also include an abstract and three to five keywords in English. The keywords must be selected from the MeSH list only, available from: https://www.ncbi.nlm.nih.gov/mesh (no other keywords will be accepted).

Texts must be submitted exclusively through the Internet, using the electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

Authorship

Authors of articles published in São Paulo Medical Journal should all have contributed actively to the discussion of the study results and should review and approve the final version to be released. The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, São Paulo Medical Journal considers that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text.

All authors should create an ORCID ID record (in www.orcid.org) before submitting their article and link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names.

During submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where they work and at least two should preferably be from outside Brazil.

FORMAT

Title page (cover page)

The title page must contain:

1. Type of paper (original article, review or updating article, short communication or letter to the editor).
2. Title of the paper in English, which must be brief but informative.
3. Full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full or omitted, without using abbreviations); his/her background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or undergraduate student); and his/her position currently held (for example, Master or Doctoral Student, Assistant Professor, Associate Professor or Professor, but not Head of Department, Dean, Provost or Rector), in the department and institution where he/she works, and the city and country (affiliations).
4. Place where the work was developed.
5. Date and venue of the event at which the paper was presented, if applicable, such as congresses or dissertation or thesis presentations.
6. Sources of support in the forms of finance for the project, study bursaries or funding for purchasing equipment or drugs. The protocol number for the funding must be presented.
7. For Brazilian authors, all grants that can be considered to be related to production of the manuscript must be declared, such as fellowships for undergraduate, master and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors, such as awards for established investigators (*Produtividade* - CNPq), accompanied by the respective grant numbers.
8. Description of any conflicts of interest held by the authors. We recommend that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest.
9. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). The author should also indicate a postal address, e-mail address and telephone number that can be published together with the article.

Main document

Second page: abstract and keywords

The second page must include the title and a 250-word abstract in English (case reports with 100 words). Do not cite references in the abstract.

Use the following headings:

1. Background: Describe the rationale for the study including the research question or the scientific hypothesis.
2. Design and setting: Declare study design correctly,[11] and the setting.
3. Methods: Describe methods briefly.
4. Results: Describe primary results with quantitative results describing the sampling strategy.
5. Conclusions: Make a succinct statement of data interpretation answering the research question presented previously.
6. Clinical Trial Registration. Mandatory for clinical trials, optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.

Insert 3 to 5 key words after the abstract, with terms differing from the title. The words must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.

Text

- Typical main headings include Introduction, Methods, Results, Discussion and Conclusion. The authors can use short subheadings too.
- Number the pages.

- Abbreviations must be avoided.
- A maximum of 3000 words in the main text, from the Introduction to the Conclusions; 1000 words for short communications.
- Maximum number of figures and/or tables is 5
- Maximum number of references is 35 (except for systematic reviews).

References

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

The reference list should be inserted after the conclusions and before the tables and figures. 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 a computer internet browser, the journal's readers will be taken to the exact document cited, and not to a general website.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent a resolution of 300 DPI and/or minimum size of 2500 pixels (width) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint or Microsoft Word documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Graphs prepared in Microsoft Excel (do not send them in image formats) spreadsheets must be accompanied by the tables of data from which they have been generated.

All the figures and tables should be cited in the text.

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 reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded to indicate the magnification used. The staining agent should be specified in the figure legend.

Original articles

Clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis, are considered to be full-text original articles, with a maximum of 3000 words.

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles.

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion). The abstracts in short communications should not be structured and have a maximum of 100 words.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement[5,6]
2. Clinical trials: CONSORT Statement[2]
3. Accuracy studies on diagnostic tests: STARD Statement[8,9]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]
5. Case reports: CARE[7]

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials have only been accepted for publication if they have received an identification number from one of the clinical trial registers (the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Short communications, case reports, case series and narrative reviews

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion), a maximum of five references and one figure or table. They should be structured in the same way as original articles. Individual case reports should contain the following sections: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

Both short communications and case reports must be submitted with abstracts and keywords. The abstracts in short communications should not be structured and have a maximum of 100 words.

The São Paulo Medical Journal is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[11] The search strategy for each database and the number of articles obtained from each database must be shown in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms are appropriate to be utilized for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT) the search dates should be indicated in the text or in the table.

Narrative reviews may be accepted by the São Paulo Medical Journal provided that a systematic search is made, and they should be structured as Original Articles. The search strategy and results should be presented as described above for case reports. By invitation from the Editor-in-Chief, narrative reviews addressing historical personal or collective experiences relating to clinical health sciences, epidemiology and public health may be accepted, but with no more than two authors.

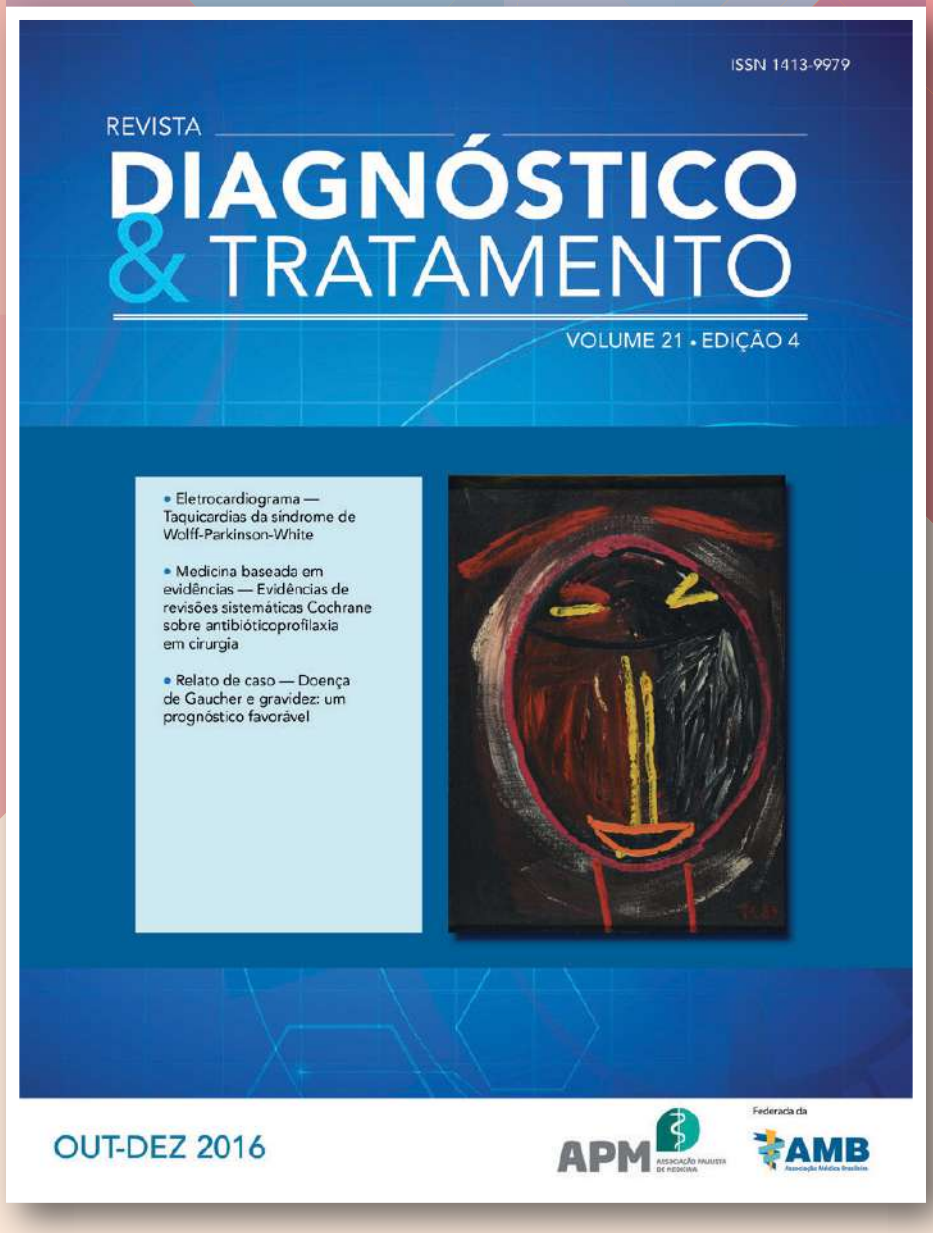
Individual case reports should contain Introduction, Case Report, Discussion and Conclusion. Case reports should be structured in accordance with the norms of the CARE Statements.[7] Case reports published in São Paulo Medical Journal must be submitted with abstracts and keywords.

Letters to the editor

Letters to the editor may address articles published in the São Paulo Medical Journal 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

1. Internal Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals, writing and editing for biomedical publications. Available from: http://www.icmje.org. Accessed in 2012 (Aug 6).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/consort-statement/. Accessed in 2012 (Aug 6).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet. 1999;354(9193):1896-900. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(99)04149-5/abstract. Accessed in 2012 (Aug 6).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: http://www.prisma-statement.org/index.htm. Accessed in 2012 (Aug 6).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2012 (Aug 6).
6. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: http://www.equator-network.org/reporting-guidelines/care/. Accessed in 2016 (Dec 20).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.stard-statement.org/. Accessed in 2012 (Aug 6).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90.
10. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contributors, Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed in 2012 (Dec 20).
11. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Available from: http://www.cebm.net/index.aspx?o=1047. Accessed in 2012 (Aug 6).



A Revista Diagnóstico & Tratamento está indexada na base de dados LILACS, e se baseia nas mais autênticas evidências científicas para oferecer artigos e atualização para a classe médica.

A revista também está disponível gratuitamente em aplicativo para smartphones e tablets (iOS e Android). Faça o download dos aplicativos e tenha acesso aos conteúdos ao alcance das mãos. Acesse o Portal da APM e saiba mais: **www.apm.org.br**.

DOWNLOAD

Google play

App Store

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Qualicorp 20 Vinte Anos | APM Associação Paulista de Medicina

Água, luz e plano de saúde de qualidade: não dá para ficar sem.

Você sabe, ter plano de saúde nos dias de hoje é item de primeira necessidade: não dá para ficar sem.

Por isso, a Qualicorp e a APM oferecem excelentes opções em condições imperdíveis para você, médico.

Planos a partir de **R$ 218**[1]

Bradesco Saúde | SulAmérica Saúde

Não fique sem plano de saúde. Ligue agora.

0800 799 3003

www.qualicorp.com.br/anuncio

Qualicorp
Sempre do seu lado.

Bradesco Saúde: ANS nº 005711 | SulAmérica: ANS nº 006246

Qualicorp Adm. de Benefícios: ANS nº 417173

[1]R$ 217,35 - Exato Adesão Trad. 16 F AHO QC COP (registro na ANS nº 476.942/16-2), da SulAmérica Saúde, faixa etária até 18 anos, com coparticipação e acomodação coletiva (tabela de julho/2017 - SP). Planos de saúde coletivos por adesão, conforme as regras da ANS. Informações resumidas. A comercialização dos planos respeita a área de abrangência da operadora de saúde. Os preços e as redes estão sujeitos a alterações, por parte da operadora de saúde, respeitadas as disposições contratuais e legais (Lei nº 9.656/98). Condições contratuais disponíveis para análise. Fevereiro/2018.

Siga a Qualicorp: