ISSN 1516-3180

São Paulo Medical Journal/Evidence for Health Care, 2023 July 6; 141(4)

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

Medline, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/ Sciences Edition (impact factor 1.838), EBSCO Publishing and PubMed Central (PMC)

July 6 - Volume 141 - Number 4

Editorial

- 500th Lung Transplantation of the Faculdade de Medicina da Universidade de São Paulo: Reflecting on Our Journey and Looking Ahead

Cross-sectional study

- Are sociodemographic and anthropometric variables effective for screening probable and confirmed sarcopenias in community-dwelling older adults?

Ecological study

- Association between exposure to air pollutants and hospitalization for SARS-Cov-2

Mill in a sunny day – Holambra (SP), Brazil
Photo: Guilherme Gomes De Mesquita - Dreamstime.com

São Paulo Medical Journal does not charge authors for publication.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Federada da AMB Associação Médica Brasileira

Global Summit
TELEMEDICINE &
DIGITAL HEALTH APM
2023

20, 21 e 22 de Novembro de 2023

Centro de Exposições Frei Caneca

Conferências e painéis **nacionais e internacionais**

5 palcos simultâneos

Tradução simultânea

+1.500 congressistas qualificados

+50 horas de conteúdo exclusivo

APROVEITE o valor de **1º LOTE**

Participe do evento

globalsummit.org.br

MÉDICO TÉCNICO RESPONSÁVEL:
DR. JEFFERSON GOMES FERNANDES CRM 143318

REALIZAÇÃO
APM
ASSOCIAÇÃO PAULISTA DE MEDICINA

São Paulo Medical Journal
EVIDENCE FOR HEALTH CARE

INDEX

Editorial

e20231414 The 500th Lung Transplantation at the Faculdade de Medicina da Universidade de São Paulo: Reflecting on Our Journey and Looking Ahead
Flavio Pola dos Reis, Paulo Manuel Pêgo-Fernandes

Original article

e202278 Smartphone and application use in self-management of chronic kidney disease: a cross-sectional feasibility study
Christielle Lidianne Alencar Marinho, Orlando Vieira Gomes, Geraldo Bezerra da Silva Junior, Paulo Adriano Schwingel

e2021771 Depressive symptoms among older adults with diabetes mellitus: a cross-sectional study
Diego Micael Barreto Andrade, Roseanne Montargil Rocha, Ícaro José Santos Ribeiro

e202285 Translation, Validity and Internal Consistency of the Quality of Dying and Death Questionnaire for Brazilian families of patients that died from cancer: a cross-sectional and methodological study
Bianca Sakamoto Ribeiro Paiva, Talita Caroline de Oliveira Valentino, Mirella Mingardi, Marco Antonio de Oliveira, Julia Onishi Franco, Michelle Couto Salerno, Helena Palocci, Tais Cruz de Melo, Carlos Eduardo Paiva

e2022210 Association between exposure to air pollutants and hospitalization for SARS-Cov-2: an ecological time-series study
Paola Cristina Ribeiro, Cristóvão José Dias da Cunha, Adriana de Oliveira Ribeiro dos Santos, Bianca Rezende Lucarevschi, Ana Cristina Gobbo César, Luiz Fernando Costa Nascimento

e2022139 Determinants of poor sleep quality in adults during the coronavirus disease pandemic: *COVID-Inconfidentes*, a population-based study
Luiz Antônio Alves de Menezes Júnior, Luciano Garcia Lourenção, Amanda Cristina de Souza Andrade, Júlia Cristina Cardoso Carraro, George Luiz Lins Machado-Coelho, Adriana Lúcia Meireles

e2022141 Are sociodemographic and anthropometric variables effective in screening probable and confirmed sarcopenia in community-dwelling older adults? A cross-sectional study
Larissa Franciny de Souza, Laís Coan Fontanela, Amanda Aparecida Oliveira Leopoldino, Vanessa Amaral Mendonça, Ana Lúcia Danielewicz, Ana Cristina Rodrigues Lacerda, Núbia Carelli Pereira de Avelar

e2022159 Prevalence risk of sarcopenia in older Brazilian adults during the pandemic: A cross-sectional analysis of the Remobilize Study
Patricia Parreira Batista, Monica Rodrigues Perracini, Juleimar Soares Coelho de Amorim, Maria do Carmo Correia de Lima, Camila Astolphi Lima, Daniele Sirineu Pereira, Renata Gonçalves Dantas, Etiene Oliveira da Silva Fittipaldi, Aurélio Dias Santos, Hércules Lázaro Morais Campos, Leani Souza Máximo Pereira

e2022323 Short-term outcomes of COVID-19 in pregnant women unvaccinated for SARS-CoV-2 in the first, second, and third trimesters: a retrospective study
Filiz Yarsilikal Guleroglu, Hatice Argun Atalmis, Icten Olgu Bafali, Gulser Bingol Dikdere, Irfan Dikdere, Murat Ekmez, Alpaslan Kaban, Fatma Karasabanoglu, Busra Seker Atas, Esra Selvi, Gulay Sumnu, Merve Topaktas, Merve Yasti Dayan, Sevilay Yavuz Dogu, Ali Cetin

e2022154 Body image in children and adolescents diagnosed with the human immunodeficiency virus: a systematic review
Suellem Zanlorenci, Andressa Ferreira da Silva, Diego Augusto Santos Silva

e2022187 Moonlighting and physician residents' compensation: is it all about money? A cross-sectional Brazilian study
Mário Luciano de Mélo Silva-Júnior, Pedro Augusto Sampaio Rocha-Filho

e2022281 Clinical and laboratory differences between chromosomal and undefined causes of non-obstructive azoospermia: A retrospective study
Luísa Riccetto, Tarsis Paiva Vieira, Nilma Lucia Viguetti-Campos, Tais Nitsch Mazzola, Mara Sanches Guaragna, Helena Fabbri-Scallet, Maricilda Palandi de Mello, Antonia Paula Marques-de-Faria, Andrea Trevas Maciel-Guerra, Gil Guerra-Junior

e2021966 Attitudes and practices in the management of attention deficit hyperactivity disorder among Brazilian pediatric neurologists who responded to a national survey: a cross-sectional study
Marina Estima Neiva Nunes, Patricia Aparecida Zuanetti, Ana Paula Andrade Hamad

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: Paulo Manuel Pêgo Fernandes, Renato Azevedo Júnior and Álvaro Nagib Atallah.
Editorial assistant: Marina de Britto.
Associate editors: Adriana Seber, Airton Tetelbom Stein, Alexander Wagner Silva de Souza, Antonio José Gonçalves, Aytan Miranda Sipahi, Cristina Muccioli, Delcio Matos, 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: Editage.
Desktop publishing: Zeppelini Publishers (www.zeppelini.com.br).
Listed in: Medline, Lilacs, SciELO, Science Citation Index Expanded and Journal Citation Reports/Sciences Edition, EBSCO publishing and PubMed Central.
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).

Scientific Council

Diretoria Executiva da Associação Paulista de Medicina (Triênio 2020-2023)

The 500th Lung Transplantation at the Faculdade de Medicina da Universidade de São Paulo: Reflecting on Our Journey and Looking Ahead

Flavio Pola dos Reis[I], Paulo Manuel Pêgo-Fernandes[II]

Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, BR

[I]MD. Attending Physician, Thoracic Surgery Department, Instituto do Coração, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, BR.
https://orcid.org/0000-0002-4510-1070

[II]MD, PhD. Vice Director, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, SP, BR; Full Professor, Department of Cardiopulmonology, Instituto do Coração, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, BR. Director, Scientific Department, Associação Paulista de Medicina (APM), São Paulo (SP), BR.
https://orcid.org/0000-0001-7243-5343

Lung transplantation is a widely accepted therapeutic option for the treatment of some advanced lung diseases. With current medical advances and new technologies, discussions on terminal patients and the possibility administering of a treatment option, whose objective is to increase survival or at least the quality of life of patients, are gaining more attention.[1]

WHERE WE CAME FROM

The modern transplantation era began in the early 1900s, when surgeons Alexis Carrel and Charles C. Guthrie, developed a blood vessel suturing technique and performed experimental transplants. This discovery earned them the Nobel Prize in 1912.[2]

In Brazil, the Faculdade de Medicina da Universidade de São Paulo (FMUSP) was also founded in 1912. The institution is recognized for its excellence in teaching, research, and university extension, and for its pioneering role in solid organ transplantation. In 1965, the institution had its first kidney transplant, which was the second ever in Brazil.[3] In 1967, at the Instituto do Coração (InCor), Professor Euryclides de Jesus Zerbini performed the first heart transplant in Brazil. However, transplantation techniques only significantly advanced in the 1970s, with the discovery of cyclosporine, the development of a preservation solution, and standardization of organ removal protocols. Due to this progress, the following transplantations programs were created and reactivated at the FMUSP: heart (1984), liver (1985), pancreas (1987), and lung (1989) transplants.[4]

In the 1990s, the discussion on lung transplantation involved adequate donor selection, surgical technique, diagnosis, and treatment of the primary graft dysfunction. In 2003, the progressive increase in the number of transplants led to the creation of an exclusive team to care for and follow-up transplant patients at the FMUSP InCor. Our team includes thoracic surgeons, pulmonologists, infection disease specialists, nurses, physiotherapists, nutritionists, social workers, and psychologists, who help patients on the waiting list and in the postoperative period.

Exactly 110 years after the FMUSP was founded, the Hospital das Clínicas InCor performed its 500th lung transplant, a milestone for thoracic surgery in Brazil and Latin America.

The InCor lung transplant group performed numerous procedures that mark the history and development of transplantation in Brazil. In 2003, we performed the first bilateral lung transplant; in 2006, the first pediatric transplant; in 2011, the first split; and in 2012, the first transplant using the ex-vivo lung perfusion technique. In 2012, we used extracorporeal membrane oxygenation (ECMO) to treat a primary graft dysfunction in a postoperative patient. Currently, 11 years after the transplant, the patient is still being followed-up as an outpatient by the group.[5]

Another important milestone was the creation of Medical Residency in Lung Transplantation for pulmonologists and thoracic surgeons, which was accredited by the National Medical Residency Commission in 2010. Most of our former students currently work in the field of lung transplantation in Brazil.

Currently, Brazil ranks second worldwide among countries that perform the highest number of transplants; moreover, Brazil has the highest public funding for this procedure, as approximately 95% of transplants in the country are funded by the Unified Health System.[3]

Our greatest challenge is to provide health care to patients who have to wait for up to 2 years to get a lung; unfortunately, the natural progression of lung disease does not often allow for such

a lengthy waiting time. We began a discussion on how to prioritize patients on the list among transplant groups in the State of São Paulo. However, after analyzing data from the last 10 years, we observed that a key component of the problem was the low organ use rate of less than 5%; in the United States and in Toronto (Canada) the rates are approximately 20% and 30%, respectively.[3] Another important information is the rate of refusal of relatives to donate organs, which according to the Brazilian Transplant Registry, occurs in up to 42% of cases.

The InCor certainly has the professional and institutional capacity to double the current organ use rate; however, it needs funding and public policies to increase the rate of consent for organ donation, and improve donor management and care.

LEARNINGS

Telemedicine has been a focal point of discussion in the medical field. Adequate use of technology can favor the population, as we live in a continental country that has few active lung transplantation services. Before the COVID-19 pandemic, lung transplantation groups used telemedicine in two main pillars: the assistant team and the patient. In the assistant team, physicians who needed to discuss cases to assess whether there was an indication for transplantation could easily consult their colleagues. Regarding the patient, contact is first made to assess the case and whether there is an indication for transplantation. If an indication was identified, a face-to-face evaluation was then scheduled.

During the pandemic, there was no discussion about lung transplantation in acute illness. In these cases, the patient's assistant team had a tele-consultation with a pulmonologist and a thoracic surgeon. If there was an indication, the patient was then transferred to the InCor to commence the specific evaluation.[6]

The management of a patient with terminal lung disease is complex as they have to be evaluated by a multidisciplinary team and, our group believes that a palliative care professional must be present to determine the patient's therapeutic plan. All patients referred for lung transplant evaluation will also be evaluated by the palliative care group to determine the guidelines. All patients referred for lung transplant evaluation will also be evaluated by the palliative care group to determine the guidelines.[7]

WHERE ARE WE HEADED

Institutions with a lung transplant program need resources and investments to continue evolving and providing quality care for patients. In 2022, the FMUSP InCor created a biobank, with a capacity of more than 84,000 samples, that could store samples at -80 °C. The progressive use of artificial intelligence and the intersection between the collected materials, associated with retrospective or prospective donor information, has also facilitated personalized care, in addition to being at the frontier of knowledge.

Institutional support is the foundation for the development and continuity of the Transplantation Program. In 2013, an important step was taken with the creation of the InCor Transplantation Center, which included the formation of a multidisciplinary team dedicated to the care of transplant patients. Owing to this structure and support, in 2022, in spite of the COVID-19 pandemic we performed 62 adult heart transplants, 36 lung transplants, and 13 congenital heart transplants, making a total of 111 thoracic organ transplants.

In summary, according to the words of the late Prof. Adib Jatene, "I do not believe in people who save, but in structures that work." Thus, as a pioneer transplantation institution at national and international levels, this program completed 500 lung transplants with a dedicated, super-specialized, multidisciplinary, and interdisciplinary team that achieved the best possible results, comparable to those of other international groups, and have allowed several patients to return to the society with an improved quality of life.

REFERENCES

1. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 202140(11):1349-79. PMID: 34419372; https://doi.org/10.1016/j.healun.2021.07.005.
2. MLA style: Alexis Carrel – Nobel Lecture - NobelPrize.org. Nobel Prize Outreach AB 2023. Mon. 3 Apr 2023. Available from: https://www.nobelprize.org/prizes/medicine/1912/carrel/lecture/. Accessed in 2023 (Apr 3).
3. Pêgo-Fernandes PM, Pestana JOM, Garcia VD. Transplants in Brazil: where are we? Clinics (Sao Paulo). 2019;74:e832. PMID: 31116230; https://doi.org/10.6061/clinics/2019/e832.
4. Stolf NAG. History of heart transplantation: A hard and glorious journey. Braz J Cardiovasc Surg. 2017;32(5):423-7. PMID: 29211224; https://doi.org/10.21470/1678-9741-2017-0508.
5. Pêgo-Fernandes PM, Hajjar LA, Galas FR, et al. Respiratory failure after lung transplantation: extra-corporeal membrane oxygenation as a rescue treatment. Clinics (Sao Paulo). 2012;67(12):1529-32. PMID: 23295616; https://doi.org/10.6061/clinics/2012(12)32.
6. Pola dos Reis F, Fernandes LM, Abdalla LG, et al. Brazilian initial experience with lung transplantation due to irreversible lung fibrosis post-COVID-19 in a national reference center: a cohort study. S Paulo Med J. 2022;140(1):153-62. PMID: 34932782; https://doi.org/10.1590/1516-3180.2021.0842.R1.13102021.
7. Lima JS, Gabriel J, Lima SR, et al. Diretivas antecipadas da vontade: autonomia do paciente e segurança profissional (Advance Directives: patient autonomy and professional safety). Rev Bioetica. 2022;30(4):769-79. Available from: https://revistabioetica.cfm.org.br/index.php/revista_bioetica/article/view/3220/3059. Accessed in 2023 (Apr 3).

Smartphone and application use in self-management of chronic kidney disease: a cross-sectional feasibility study

Christielle Lidianne Alencar Marinho[I], Orlando Vieira Gomes[II], Geraldo Bezerra da Silva Junior[III], Paulo Adriano Schwingel[IV]

Universidade de Pernambuco (UPE), Recife (PE), Brazil

[I]MSc. Nurse and Doctoral Student, Health Sciences Program, Universidade de Pernambuco (UPE), Recife (PE), Brazil.
https://orcid.org/0000-0002-3827-5494

[II]MD, MSc. Nephrologist and Assistant Professor, School of Medicine, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil.
https://orcid.org/0000-0001-6324-7594

[III]MD, PhD. Physician and Professor, Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará (UFC), and School of Medicine, Public Health and Medical Sciences Graduate Programs, Universidade de Fortaleza (UNIFOR), Fortaleza (CE), Brazil.
https://orcid.org/0000-0002-8971-0994

[IV]PhD. Sports Physiologist and Associate Professor, Human Performance Research Laboratory, Universidade de Pernambuco (UPE), Petrolina (PE), Brazil.
https://orcid.org/0000-0002-2935-3403

KEYWORDS (MeSH terms):
Renal insufficiency, chronic.
Treatment adherence and compliance.
Smartphone.
Self-management.
Dialysis.

AUTHOR'S KEYWORDS:
Kidney disease.
Health technology.
Telehealth.
Health monitoring.
Digital health.

ABSTRACT

INTRODUCTION: Smartphone and application use can improve communication and monitoring of chronic diseases, including chronic kidney disease, through self-management and increased adherence to treatment.

OBJECTIVE: To assess smartphone use in patients with chronic kidney disease on dialysis and their willingness to use mobile applications as a disease self-management strategy.

DESIGN AND SETTING: This was a cross-sectional study of chronic kidney disease patients on hemodialysis in the São Francisco Valley in the Northeast Region, Brazil.

METHODS: The questionnaire developed by the authors was administered between April and June 2021. Cronbach's alpha coefficient for the construct was 0.69. Associations between the dependent and independent variables were determined using univariate analysis. Multivariate analysis with logistic regression analysis was also performed.

RESULTS: A total of 381 patients were included, of whom 64% had a smartphone, although only 3.1% knew of a kidney disease-related application. However, 59.3% believed that using an application could help them manage their disease. Having a smartphone was associated with treatment adherence, higher educational attainment, and higher per capita income. Educational attainment remained an independent factor in multivariate analysis.

CONCLUSION: More than 64% of patients had a smartphone, although few knew of applications developed for kidney disease. More than half of the population believed that technology use could benefit chronic kidney disease treatment. Smartphone ownership was more common among the younger population, with higher educational attainment and income, and was associated with greater adherence to hemodialysis sessions.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, with approximately 10% of the world population having some degree of CKD. It has significant social and financial implications for both developed and developing countries.[1-3]

International estimates further indicate that the number of people who need renal replacement therapy (RRT) will increase from 2,618 million in 2010 to 5,439 million by 2030.[4] However, not everyone who needs RRT can access the treatment, because it is not universally covered worldwide.[5] In Brazil, RRT is universally covered by the Unified Health System. According to the Brazilian Society of Nephrology, the estimated number of new patients undergoing dialysis in 2019 was 45,852 – a 7.7% increase from 2018, along with a 3.9% mean increase in CKD prevalence in the same period.[6]

Adherence to treatment poses an immense challenge for patients with CKD, their relatives, and health teams. The importance of individualized care has been emphasized, including realistic patient-centered goals and shared decision-making between the health team and patient. For this strategy to be effective, the patient's cognitive function, health knowledge, socioeconomic factors, and treatment experiences must be considered.[7,8]

Hence, a viable alternative is to align therapeutic strategies with effervescent technological growth and include this as a tool to achieve better health outcomes via mobile health (mHealth). According to the International Telecommunication Union, 66.6% of the world's population were using mobile Internet at the beginning of 2021. The number of smartphones in use has increased by 7% per year, with an average of more than one million new smartphones coming into use every day.[9]

Even though health technology is used in high-income countries, the widespread use and accessibility of mobile phones have enabled its proliferation in low- and medium-income countries, thereby reaching more people in limited-resource settings.[10] Recent studies show that mobile devices have improved regular communication and monitoring between health professionals and their patients, as well as adherence to medication use and lifestyle changes.[11-13]

The coronavirus disease 2019 (COVID-19) pandemic has caused rapid unprecedented growth in the use of technology in the health field. However, barriers and challenges–such as patients' lack of knowledge and Internet connectivity, health professionals' limited competence in mHealth, and financial challenges–can hinder the adoption of such interventions.[14]

Thus, to obtain optimal results with this tool, it is important to know the target population of the technology, understand the current limitations, and assess the individuals' knowledge of this resource and willingness to use it.

OBJECTIVE

The objective of this study was to assess the use of smartphones by CKD patients on dialysis and their willingness to use mobile applications as a strategy for disease self-management.

METHODS

This was an analytical cross-sectional quantitative study of CKD patients on hemodialysis at a renal treatment reference service in the São Francisco Valley, in the Northeast Region of Brazil.

The eligibility criteria were as follows: age ≥ 18 years and undergoing treatment for > 3 months. Individuals who reported cognitive deficits in their medical records or self-reported disabilities that prevented them from answering the research questions were excluded. A total of 443 patients were registered at the dialysis center, 401 of whom were eligible to participate in the study. Twenty individuals did not agree to participate; therefore, the sample included 381 subjects.

Data were collected using a questionnaire developed by the authors regarding sex, age, marital status, religion, skin color/race, educational attainment, per capita income, hemodialysis time in treatment, kidney disease etiology, associated diseases, use of smartphones, use of applications, use and knowledge of applications for CKD, use of additional tools to cope with and manage the disease, and non-attendance at dialysis sessions in the previous month (https://doi.org/10.6084/m9.figshare.20051600). The instrument to assess the use of mobile technologies in the treatment of CKD was evaluated three times. Research on reliability and reproducibility involved 10 patients, aged 40 to 75 years, undergoing hemodialysis. The instrument items were assessed using Cronbach's alpha for internal consistency. The instrument's reliability was measured by calculating the agreement and estimating kappa coefficients. The Cronbach's alpha coefficient for the construct was 0.687, demonstrating moderate reliability in the three small-group assessments. The supplementary material available at https://doi.org/10.6084/m9.figshare.20051600 analyzes the individual questions and demonstrates maximum agreement values (1.00) for 10 of the 15 questions. In addition, all questions in the instrument demonstrated very high reliability, with values of > 0.90.

Data were collected between April and June 2021 via interviews conducted by trained researchers. Interviews were conducted in a dialysis room while the patients were undergoing treatment. On the day of the interview, a trained researcher conducted a structured face-to-face interview using a standardized questionnaire (SM1) with suitable space for each patient. The patients were asked direct questions and the responses were classified by the interviewer according to the alternatives in the questionnaire.

The answers were typed and stored in regular Excel spreadsheets (Microsoft Corporation, Redmond, Washington, United States, Release 12.0.6662, 2012) and exported to the SPSS computer program (SPSS Inc., Chicago, Illinois, United States, Release 16.0.2, 2008). Descriptive statistical analysis was performed with categorical variables presented as absolute and relative frequencies. Continuous variables were reported as mean ± standard deviation (SD) after data normality was determined using the Kolmogorov-Smirnov test. For inferential analysis, continuous data were analyzed using the Student's t-test for independent samples or one-way analysis of variance. Age and mobile phone use were correlated using Pearson's correlation coefficient. In the univariate analysis, the association between the dependent variable (having a smartphone) and each independent variable (sex, marital status, age group, religion, skin color/race, educational attainment, income, time in treatment, and non-attendance to dialysis) was calculated using Pearson's chi-square test or Fisher's exact test. Variables with $P \leq 0.20$ in these analyses were selected for multivariate analysis with logistic regression, performed with the stepwise technique. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Statistical analyses were two-tailed, and statistical significance was set at $P < 0.05$.

The Research Ethics Committee of the Amaury de Medeiros Integrated Health Center (CISAM, in Portuguese) approved this research on May 20, 2020, under register number 4.044.382 (CAAE:31246220.1.0000.5191). The participants were informed of the study objective and the procedures they would undergo. Participants then signed an informed consent form agreeing to their voluntary participation in the research.

RESULTS

The patients' ages ranged from 19 to 92 years, with a mean age (± SD) of 50.8 (± 16.0) years. Most participants were male (n = 240; 63.0%), had completed middle school (n = 129; 33.3%), and earned

an income ranging from one to two times the minimum wage (n = 286; 75.1%). The minimum wage at the time was R$ 1,100.00 (US$ 202.00). The sample characteristics are listed in **Table 1**.

Although more than 64% of participants had smartphones, only 12 (3.1%) knew about kidney disease-related applications (**Table 2**). The proportion of kidney patients on hemodialysis who used additional treatment strategies was 14.4% (95% CI: 11.1–18.4). However, approximately 60% of the patients considered that using a mobile application could help manage kidney disease.

Having a smartphone was associated with adherence to treatment, higher educational attainment, and higher per capita income (**Table 3**). The mean age of the patients who had a smartphone (44.7 ± 13.5 years) was statistically lower (P < 0.001) than that of the patients who did not have one (61.7 ± 14.2 years).

Moreover, according to the OR calculated for the association of baseline characteristics with mobile phone use, only educational attainment remained an independent factor in smartphone

Table 1. Sample characterization. São Francisco Valley, Brazil, 2021 (n = 381)

Variables	n	%	95% CI
Sex			
Female	141	37.0%	32.2–42.1
Male	240	63.0%	58.0–67.7
Age			
≤ 44 years	143	37.5%	32.8–42.5
45–64 years	157	41.2%	36.4–46.2
65–74 years	48	12.6%	9.6–16.3
≥ 75 years	33	8.7%	6.2–11.9
Marital status			
Single	102	26.8%	22.4–31.5
Married	206	54.1%	48.9–59.2
Divorced	39	10.2%	7.4–13.7
Widow(er)	34	8.9%	6.3–12.3
Religion			
Catholic	244	64.0%	59.0–68.9
Evangelical	110	28.9%	24.4–33.7
Others	13	3.4%	1.8–5.8
No religion	14	3.7%	2.0–6.1
Race/skin color			
Multiracial	256	67.2%	62.2–71.9
Black	53	13.9%	10.6–17.8
White	72	18.9%	15.1–23.2
Educational attainment			
Illiterate, or elementary school not completed	82	21.5%	17.5–26.0
Elementary school completed and/or middle school not completed	129	33.9%	29.1–38.9
Middle school completed and/or high school not completed	58	15.2%	11.8–19.2
High school completed and/or higher education not completed	94	24.7%	20.4–29.3
Higher education completed	18	4.7%	2.8–7.4
Per capita income			
Less than 1 time the minimum wage (< US$ 200.00)	58	15.2%	11.8–19.2
From 1 to 2 times the minimum wage (from U$ 200.00 to 400.00)	286	75.1%	70.4–79.3
From 3 to 5 times the minimum wage (> U$ 400.00 to 1,000.00)	25	6.6%	4.3–9.5
More than 5 times the minimum wage (> U$ 1,000.00)	12	3.1%	1.6–5.4
Time in treatment			
Less than 1 year	77	20.2%	16.2–24.60
From 1 to 2 years	88	23.1%	19.0–27.7
From 3 to 5 years	101	26.5%	22.1–31.2
From 5 to 10 years	69	18.1%	14.4–22.4
More than 10 years	46	12.1%	9.0–15.8
Non-attendance to treatment sessions in the previous month			
Yes	72	18.9%	15.1–23.2
No	309	81.1%	76.8–84.9

CI = confidence interval.

acquisition (**Table 4**). In addition, the other clinical variables analyzed were not related to mobile phone use nor to kidney disease-related mobile applications.

DISCUSSION

Few studies have assessed the use of innovative technologies, including smartphones and applications, as auxiliary methods for treating CKD patients to increase their treatment adherence. Low adherence to CKD treatment has been associated with a greater probability of disease progression and higher mortality.[15] The study participants were predominantly male, multiracial, married, catholic, with low educational attainment and low income. This reflects the epidemiological profile of the Brazilian population on dialysis. Approximately 65% of the studied patients had a smartphone, and more than half of them used applications in their daily routine. The most used applications were social media, such as WhatsApp, Facebook, and Instagram. Few participants knew of an application to help with kidney treatment. However, more than half of the participants still considered it important and believed it could help them to manage their health conditions. Moreover, smartphone use was associated with income, educational attainment, and adherence to hemodialysis treatment.

A global study investigated CKD epidemiology in 2017 and found a higher prevalence of women in the initial stages of CKD, whereas there were more men in the final stages; moreover, the mortality rates were higher among men.[16] This may be explained by the harmful effects of testosterone combined with unhealthy lifestyles among men, accelerating their decline in kidney function.

The mean age of the study population was 50.8 years, corroborating other studies conducted in Brazil, wherein the most prevalent age range was from 50 to 60 years.[17] In a study conducted in Iceland, the mean age of patients with terminal CKD was 63 years, while in another study of 1,174 individuals from Sri Lanka, the mean age was 58.7 years.[18,19]

Studies on CKD conducted both within Brazil and in other countries found similar economic profiles and educational attainments to the present study population. Socially disadvantaged people worldwide face a disproportionate kidney disease burden.[2,6,20,21] It is important to understand the educational and economic situation of patients who are receiving care to provide them with effective treatment.

Recent technological advancements, combined with the COVID-19 pandemic, have led more people to embrace the alternatives offered by virtual media. Hence, technology that was exclusive to developed countries and economically advantaged people

Table 2. Use and knowledge of mobile phones. São Francisco Valley, Brazil, 2021 (n = 381)

Variables	n	%	95% CI
Have a smartphone			
Yes	245	64.3%	59.3–69.1
No	136	35.7%	30.1–40.7
Applications installed			
Yes	209	54.9%	49.7–59.9
No	25	6.6%	4.3–9.5
Do not know what an application is	11	2.9%	1.5–5.1
Do not have a smartphone	136	35.7%	30.9–40.7
Knows of kidney disease-related applications			
Yes	12	3.1%	1.6–5.4
No	369	96.9%	94.6–98.4
Believes that mobile applications may help manage the kidney disease			
Yes	226	59.3%	54.2–64.3
No	55	14.4%	11.1–18.4
Do not know	100	26.2%	21.9–31.0
Uses treatment strategies other than dialysis			
Yes	55	14.4%	11.1–18.4
No	326	85.6%	81.6–88.9
Additional strategies used			
Physical activity	18	4.7%	2.8–7.4
Physical therapy	7	1.8%	0.7–3.8
Nutritional therapy	4	1.0%	0.3–2.7
Psychological therapy	15	3.9%	2.2–6.4
Religion/Spirituality	4	1.0%	0.3–2.7
Various therapies	7	1.8%	0.7–3.8
Does not use additional strategies	326	85.6%	81.6–88.9

CI = confidence interval.

Table 3. Relationship between sociodemographic characteristics, clinical variables, and mobile phone use. São Francisco Valley, Brazil, 2021 (n = 381)

Variables	Has a smartphone				P
	Yes (n = 245)		No (n = 136)		
	n	%	n	%	
Sex					
Female	95	38.8%	46	33.8%	0.337
Male	150	61.2%	90	66.2%	
Marital status					
Single	74	30.2%	28	20.6%	< 0.001
Married	138	56.3%	68	50.0%	
Divorced	22	9.0%	17	12.5%	
Widowed	11	4.5%	23	16.9%	
Religion					
Catholic	150	61.2%	94	69.1%	0.104
Evangelical	73	29.8%	37	27.2%	
Others	9	3.7%	4	2.9%	
No religion	13	5.3%	1	0.7%	
Race/skin color					
Multiracial	163	66.5%	93	68.4%	0.896
Black	34	13.9%	19	14.0%	
White	48	19.6%	24	17.6%	
Educational attainment					
Illiterate, or elementary school not completed	24	9.8%	58	42.6%	< 0.001
Elementary school completed and/or middle school not completed	77	31.4%	52	38.2%	
Middle school completed and/or high school not completed	43	17.6%	15	11.0%	
High school completed and/or higher education not completed	84	34.3%	10	7.4%	
Higher education completed	17	6.9%	1	0.7%	
Per capita income					
Less than 1 time the minimum wage (< US$ 200.00)	40	16.3%	18	13.2%	0.043
From 1 to 2 times the minimum wage (from U$ 200.00 to 400.00)	174	71.0%	112	82.4%	
From 3 to 5 times the minimum wage (> U$ 400.00 to 1,000.00)	21	8.6%	4	2.9%	
More than 5 times the minimum wage (> U$ 1,000.00)	10	4.1%	2	1.5%	
Time in treatment					
Less than 1 year	48	19.6%	29	21.3%	0.830
From 1 to 2 years	60	24.5%	28	20.6%	
From 3 to 5 years	67	27.3%	34	25.0%	
From 5 to 10 years	42	17.1%	27	19.9%	
More than 10 years	28	11.4%	18	13.2%	
Non-attendance to treatment sessions in the previous month					
Yes	37	15.1%	35	25.7%	0.011
No	208	84.9%	101	74.3%	

Table 4. Odds ratios of the association between baseline characteristics and mobile phone use. São Francisco Valley, Brazil, 2021 (n = 381)

Variables	Smartphone use				Odds ratio	
	Yes (n = 245)		No (n = 136)		Crude (95% CI)	Adjusted (95% CI)
	n	%	n	%		
Marital status						
Single, divorced or widowed	107	43.7%	68	50.0%	1.00	1.00
Married	138	56.3%	68	50.0%	1.38 (0.88–2.17)	1.29 (0.85–1.96)
Educational attainment						
Illiterate to middle school completed	144	58.8%	125	91.9%	1.00	1.00
High school to higher education completed	101	41.2%	11	8.1%	7.97 (4.09–15.52)	7.70 (3.80–15.01)
Per capita income						
2 times the minimum wage or less (≤ U$ 400.00)	214	87.3%	130	95.6%	1.00	1.00
More than 2 times the minimum wage (> U$ 400.00)	31	12.7%	6	4.4%	1.00 (0.36–2.80)	1.08 (0.39–3.00)
Non-attendance to treatment sessions in the previous month						
Yes	37	15.1%	35	25.7%	1.00	1.00
No	208	84.9%	101	74.3%	0.65 (0.37–1.12)	0.64 (0.36–1.11)

CI = confidence interval.

has become accessible and desired by a larger significant portion of the population.[22]

A study of 949 patients on dialysis in the United States showed that 81% of them had smartphones, 72% reported using the Internet, and 60% were interested in using mHealth to manage their health.[23] Another study conducted on patients on dialysis in Australia found that 83.5% of them had mobile phones, although only 36.6% used applications.[24] In the present study, this percentage was smaller, which points to the lower purchasing power of patients on dialysis in Brazil. Nevertheless, despite not knowing about any CKD applications, the patients believed that CKD applications could be effective.

One barrier to the implementation of this technology is the limited knowledge of the potential benefits of CKD applications for both users and health professionals. While health professionals recognize the potential of CKD applications, they lack the knowledge, time, and skill to search, assess, and recommend reliable applications, thus highlighting that these technologies need support policies and better publicization.[25]

Health teams must be trained to both use and encourage the use of applications, as they are agents who promote health education, and whom patients trust.[10] There are Portuguese applications aimed at CKD patients; for example, Renal Health, which has multiple tools such as a smart medication box with reminder alarms, monthly examination charts, liquid and diet control, and general information on kidney disease.[26]

Age, marital status, educational attainment, and income were associated with smartphone use. Younger, single people with higher educational attainment and income tend to have smartphones, in contrast to older, married individuals with lower educational attainment and income. These results corroborate those of other studies in which age, educational attainment, and income were factors associated with smartphone use.[23,27,28]

A primary objective of introducing mobile phone use to promote health self-management is to increase treatment adherence. Patients with CKD must adhere to four treatment pillars: hemodialysis, restricted fluid intake, diet, and medication use. Regarding hemodialysis, only 18.9% of the participants in this study were non-adherent to therapy. Smartphone use was associated with treatment adherence. Thus, it can be inferred that mobile phone use is an interesting tool for increasing adherence. Despite not using specific CKD applications, participants belonged to instant message groups that exchanged information on the disease, its treatment, difficulties, and challenges (data not shown). These platforms allow them to share their afflictions and experiences, generating empathy and consequently energy to continue the treatment.[29] A systematic review demonstrated that 70% of the studies reported statistical associations between social support and adherence to treatment; moreover, other studies identified social and family support as protective factors against non-adherence to treatment.[30]

Generally, adhering to a given treatment is similar to acquiring a new habit in which information is obtained and incorporated into the routine. However, understanding the person's perceptions and difficulties and becoming acquainted and establishing ties with them simplifies this process.[31]

The possibility of introducing mobile technology into the routine of patients with CKD is very promising, as it can potentially add knowledge and empowerment to their treatment. The patients were interested in this possibility; therefore, health services that treat them should encourage application use and provide the necessary information to promote the technology, including monthly examination results, limits of the liquid they can drink, diet, and medication prescriptions.

Thus, it is important to identify individuals with greater difficulties and barriers to technological access. This will help in allowing mHealth interventions to equitably reach as many people as possible. Application developers must consider the needs of both older adults and those with low literacy to diminish the digital gap between users and non-users. Hence, campaigns to enable older adults to use mobile technologies and increase their health literacy may help to reduce the inequalities caused by technological progress.[32]

Few studies have addressed CKD patients and their interest in and use of smartphones to help promote health among these individuals in Brazil, which makes this research relevant as a bridge to efficiently implementing such resources in the country. A limitation of this study is the single-period and single-service data collection. Thus, although the associations between the variables were assessed, causality between them was not.

CONCLUSION

More than 64% of CKD patients on dialysis treatment had a smartphone, and 54.9% used applications. Although few patients knew of applications aimed at kidney disease, more than half of them believed that such technology use may benefit CKD treatment. Having a smartphone was more frequent among younger patients with higher educational attainment and income and was also associated with greater adherence to hemodialysis sessions.

REFERENCES

1. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017;21;390(10105):1888-1917. PMID: 28434650; https://doi.org/10.1016/S0140-6736(17)30788-2.
2. Crews DC, Bello AK, Saadi G. 2019 World Kidney Day Editorial - burden, access, and disparities in kidney disease. J Bras Nefrol. 2019;41(1):1-9. PMID: 31063178; https://doi.org/10.1590/2175-8239-JBN-2018-0224.

3. Jonsson AJ, Lund SH, Eriksen BO, Palsson R, Indridason OS. The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds. Kidney Int. 2020;98(5):1286-95. PMID: 32622831; https://doi.org/10.1016/j.kint.2020.06.017.
4. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. Nat Rev Nephrol. 2020;16(10):573-85. PMID: 32733095; https://doi.org/10.1038/s41581-020-0315-4.
5. Assis Buosi AP, Paturkar D, Dias ER, et al. The Rights of Patients with Chronic Kidney Disease in the World: Legal Perspectives and Challenges in Brazil, India, Portugal, South Africa, and Nigeria. Contrib Nephrol. 2021;199:322-38. PMID: 34344007; https://doi.org/10.1159/000517722.
6. Neves PDMM, Sesso RCC, Thomé FS, Lugon JR, Nascimento MM. Inquérito Brasileiro de Diálise Crônica 2019. Braz J Nephrol. 2021;43(2):217-27. https://doi.org/10.1590 / 2175-8239-JBN-2020-0161.
7. Acar D, Güneş Z. Factors affecting therapeutic compliance in patients with chronic renal failure: Anxiety, Depression, Illness Perception. Health Prim Care. 2018;2(3):1-6. https://doi.org/10.15761/HPC.1000137.
8. Chan CT, Blankestijn PJ, Dember LM, et al. Dialysis initiation, modality choice, access, and prescription: conclusions from a kidney disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;96(1):37-47. PMID: 30987837; https://doi.org/10.1016/j.kint.2019.01.017.
9. International Telecommunication Union. ITU Statistics Retrieved from. 2021. Available from: https://www.itu.int/en/ITU-D/Statistics/Pages/stat/default.aspx. Accessed in 2022 (Apr 28).
10. Osei E, Mashamba-Thompson TP. Mobile health applications for disease screening and treatment support in low-and middle-income countries: A narrative review. Heliyon. 2021;7(3):e06639. PMID: 33869857; https://doi.org/10.1016/j.heliyon.2021.e06639.
11. Harding K, Biks GA, Adefris M, et al. A mobile health model supporting Ethiopia's eHealth strategy. Digit Med. 2018;4(2):54-65. PMID: 31608321; https://doi.org/10.4103/digm.digm_10_18.
12. Jemere AT, Yeneneh YE, Tilahun B, et al. Access to mobile phone and willingness to receive mHealth services among patients with diabetes in Northwest Ethiopia: a cross-sectional study. BMJ Open. 2019;9(1):e021766. PMID: 30679284; https://doi.org/10.1136/bmjopen-2018-021766.
13. Abolfotouh MA, BaniMustafa A, Salam M, et al. Use of smartphone and perception towards the usefulness and practicality of its medical applications among healthcare workers in Saudi Arabia. BMC Health Serv Res. 2019;19(1):826. PMID: 31718639; https://doi.org/10.1186/s12913-019-4523-1.
14. Kruse C, Betancourt J, Ortiz S, et al. Barriers to the Use of Mobile Health in Improving Health Outcomes in Developing Countries: Systematic Review. J Med Internet Res. 2019;21(10):e13263. PMID: 31593543; https://doi.org/10.2196/13263.
15. Cedillo-Couvert EA, Ricardo AC, Chen J, et al. CRIC Study Investigators. Self-reported Medication Adherence and CKD Progression. Kidney Int Rep. 2018;3(3):645-51. PMID: 29854972; https://doi.org/10.1016/j.ekir.2018.01.007.
16. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33. PMID: 32061315; https://doi.org/10.1016/S0140-6736(20)30045-3.
17. Andrade AS, Lima JS, Inagaki AD, et al. Fatores associados à qualidade de vida de pacientes submetidos à hemodiálise. Enferm Foco. 2021;12(1):20-5. https://doi.org/10.21675/2357-707X.2021.v12.n1.3451.
18. Jonsson AJ, Lund SH, Eriksen BO, Palsson R, Indridason OS. The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds. Kidney Int. 2020;98(5):1286-95. PMID: 32622831; https://doi.org/10.1016/j.kint.2020.06.017.
19. Senanayake S, Gunawardena N, Palihawadana P, et al. Health related quality of life in chronic kidney disease; a descriptive study in a rural Sri Lankan community affected by chronic kidney disease. Health Qual Life Outcomes. 2020;18(1):106. PMID: 32326945; https://doi.org/10.1186/s12955-020-01369-1.
20. Gesualdo GD, Duarte JG, Zazzetta MS, Kusumota L, Orlandi FS. Fragilidade e fatores de risco associados em pacientes com doença renal crônica em hemodiálise. Cien Saude Coletiva. 2020;25(11):4631-37 https://doi.org/10.1590/1413-812320202511.03482019.
21. Amaral TLM, Amaral CA, Vasconcellos MTL, Monteiro GTR. Doença renal crônica em adultos de Rio Branco, Acre: inquérito de base populacional [Chronic kidney disease among adults in Rio Branco, State of Acre: a population-based survey]. Cien Saude Coletiva. 2021;26(1):339-50. https://doi.org/10.1590/1413-81232020261.22402018.
22. Mariani AW, Pêgo-Fernandes PM. The impact of COVID-19 on the development and consolidation of telemedicine. Sao Paulo Med. J. 2021;139(3):199-200. PMID: 33978134; https://doi.org/10.1590/1516-3180.2021.139305042021.
23. Hussein WF, Bennett PN, Pace S, et al. The Mobile Health Readiness of People Receiving In-Center Hemodialysis and Home Dialysis. Clin J Am Soc Nephrol. 2020;16(1):98-106. PMID: 33355235; https://doi.org/10.2215/CJN.11690720.
24. Bonner A, Gillespie K, Campbell KL, et al. Evaluating the prevalence and opportunity for technology use in chronic kidney disease patients: a cross-sectional study. BMC Nephrol. 2018;19(1):28. PMID: 29394930; https://doi.org/10.1186/s12882-018-0830-8.
25. Byambasuren O, Beller E, Glasziou P. Current Knowledge and Adoption of Mobile Health Apps Among Australian General Practitioners: Survey Study. JMIR Mhealth Uhealth. 2019;7(6):e13199. PMID: 31199343; https://doi.org/10.2196/13199.
26. da Silva Junior GB, de Oliveira JGR, de Araújo EMR, et al. Renal Health: Providing Information and Technological Tools to Empower Patients to Live Better with Kidney Disease. Stud Health Technol Inform. 2021;281:674-8. PMID: 34042661; https://doi.org/10.3233/SHTI210257.

27. Ma Q, Chan AH, Chen K. Personal and other factors affecting acceptance of smartphone technology by older Chinese adults. Appl Ergon. 2016;54:62-71. PMID: 26851465; https://doi.org/10.1016/j.apergo.2015.11.015.
28. Sayed MI, Mamun-Ur-Rashid M. Factors influencing e-Health service in regional Bangladesh. Int J Health Sci (Qassim). 2021;15(3):12-9. PMID: 34234631.
29. Oliveira JGR, Askari M, Fahd MGN, et al. Chronic Kidney Disease and the Use of Social Media as Strategy for Health Education in Brazil. Stud Health Technol Inform. 2019;264:1945-6. PMID: 31438420; https://doi.org/10.3233/SHTI190726.
30. Sousa H, Ribeiro O, Paúl C, et al. Social support and treatment adherence in patients with end-stage renal disease: A systematic review. Semin Dial. 2019;32(6):562-74. PMID: 31309612; https://doi.org/10.1111/sdi.12831.
31. Chan AHY, Honey MLL. User perceptions of mobile digital apps for mental health: Acceptability and usability - An integrative review. J Psychiatr Ment Health Nurs. 2022;29(1):147-68. PMID: 33604946; https://doi.org/10.1111/jpm.12744.
32. Ernsting C, Dombrowski S, Oedekoven M, et al. Using Smartphones and Health Apps to Change and Manage Health Behaviors: A Population-Based Survey. J Med Internet Res. 2017;19(4):e101. PMID: 28381394; https://doi.org/10.2196/jmir.6838.

Authors' contributions: Marinho CLA: conceptualization (lead), data curation (equal), formal analysis (lead), investigation (equal), project administration (lead), writing-review and editing (equal), and final approval of the version to be published (equal); Gomes OV: conceptualization (equal), investigation (equal), resources (equal), writing-original draft (equal), and writing-review and editing (equal); Silva Junior GB: conceptualization (equal), data curation (equal), resources (equal), writing-original draft (equal), writing-review and editing (equal)interpretation of data for the work (equal), revising it critically for important intellectual content (lead); Schwingel PA: supervision (lead), interpretation of data for the work (equal), writing-original draft (equal), and writing-review and editing (lead). All authors actively contributed to the discussion of the study results and reviewed and approved the final version of the manuscript.

Sources of funding: Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE) [APQ-0246-4.06/14; APQ-1413-4.08/21; BIC-1434-4.06/21; BCT-0293-4.06/22], Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) [finance code 001]
Conflicts of interest: We declare that there were no competing interests

Date of first submission: January 30, 2022
Last received: June 12, 2022
Accepted: August 9, 2022

Address for correspondence:
Christielle Lidianne Alencar Marinho
R. Arnóbio Marques, 310
Santo Amaro — Recife (PE) — Brasil
CEP 50100-130
Tel. (+55 87) 99629-6477
E-mail: christiellealencar@yahoo.com.br

Depressive symptoms among older adults with diabetes mellitus: a cross-sectional study

Diego Micael Barreto Andrade[I], Roseanne Montargil Rocha[II], Ícaro José Santos Ribeiro[III]

Department of Health II, Universidade Estadual do Sudoeste da Bahia (UESB), Bahia (BA), Brazil

[I]PhD. Nurse and Professor, Faculty of Health Sciences, University of Pécs (UP), Pécs, Hungary. https://orcid.org/0000-0002-5323-1211

[II]PhD. Nurse and Full Professor, Department of Health II, Universidade Estadual de Santa Cruz (UESC), Ilhéus (BA), Brazil. https://orcid.org/0000-0001-5766-413X

[III]PhD. Nurse Researcher and Professor, Department of Health II, Universidade Estadual do Sudoeste da Bahia (UESB), Jequié (BA), Brazil. https://orcid.org/0000-0002-4389-7810

KEYWORDS (MeSH terms):
Depression.
Primary health care.
Osteoporosis.
Diabetes mellitus.
Diabetes complications.

AUTHORS' KEYWORDS:
Depressive symptoms.
Diabetic complications.
Geriatric depression.

ABSTRACT

BACKGROUND: Diabetes mellitus is a chronic disease with long-term consequences that is often associated with depressive symptoms. This relationship predicts increased morbidity and mortality rates, leading to serious health consequences.

OBJECTIVE: To identify the prevalence and health factors associated with depressive symptoms among older adults with diabetes mellitus.

DESIGN AND SETTING: An observational cross-sectional study was conducted among 236 older adults in the Basic Healthcare Units of Jequié, Brazil.

METHODS: A survey containing sociodemographic, behavioral, and health conditions was used as a data collection instrument, in addition to the Geriatric Depression Scale. The main inclusion criterion was older adults diagnosed with diabetes mellitus. To identify the risk factors associated with depressive symptoms among older adults with diabetes mellitus, logistic regression analysis was conducted for calculating the odds ratio (OR), and a 95% confidence interval (CI) was considered statistically significant.

RESULTS: The prevalence of depressive symptoms was 24.2% among older adults with diabetes, corroborating the Brazilian average of 30%. The final multivariate analysis model for the risk of depressive symptoms showed a significant association with diabetes complications [OR = 2.50, 95% CI 1.318–4.74)] and osteoporosis [OR = 2.75, 95% CI 1.285–5.891)].

CONCLUSION: A high prevalence of depressive symptoms was observed among older adults with diabetes. Critically examining older adults with diabetes mellitus is necessary, and screening for depressive symptoms is highly recommended, especially for those with complications resulting from diabetes mellitus and musculoskeletal comorbidities, such as osteoporosis, as it seems to be associated with depressive symptoms.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that primarily affects older adults. Owing to long-term consequences, such as complications of the kidneys, eyes, nerves, heart, and blood vessels, DM constitutes a major public health problem.[1,2] The prevalence of diabetes is increasing worldwide. According to the International Diabetes Federation's 2021 Diabetes Atlas, 537 million adults aged between 20 and 79 years are living with diabetes. In Brazil, estimates show that up to 16.8 million people have DM, which is approximately 7% of the population.[1]

Moreover, the presence of depressive symptoms deserves equal attention because of its increasing prevalence among community-dwelling older adults, ranging from 13% to 39%.[3] The prevalence of depressive symptoms in Jequié, Bahia, Brazil, exceeded 88% of older adults, and was mostly correlated with chronic diseases.[4] Conversely, there are high rates of depression underdiagnosis in older adults, which can increase the development of other risk factors in this population.[5-7]

Several studies have suggested an association between diabetes and depression. There are various predictors of depression among older adults with DM, such as socioeconomic, individual, behavioral, and clinical factors.[8] Depression has been reported as a risk factor for type 2 diabetes.[9,10] Meanwhile, depression is reportedly two times more prevalent in people with DM than in people who do not have diabetes.[11-13] Depression has also been linked to family dysfunction and poor health outcomes in patients with type 2 diabetes.[12,14-16]

Nonetheless, depression and diabetes represent the fourth and eighth most important causes of disability-adjusted life years, respectively.[17] Moreover, this relationship predicts increased morbidity and mortality rates, non-adherence to treatment, low quality of life, and an immense public health impact.[11,12,18-20]

Therefore, this study is important because, globally, depressive symptoms and diabetes in older adults are becoming the leading causes of disability, with greater frailty and vulnerability. Thus, the presence of depressive symptoms associated with DM can seriously impact an individual's physical health and quality of life, since both increase their risk for mortality and poor disease management. Furthermore, primary care is the gateway to identifying and monitoring individuals with DM. Thus, this study is relevant to help identify risk factors, establish early interventions, and plan appropriate care for these individuals. Our research questions were: "What is the prevalence of depressive symptoms among older adults with DM?" and "What is the relationship between depressive symptoms and health conditions in older adults?" We hypothesized that a significant proportion of depressive symptoms among older adults with DM would be related to their health status.

OBJECTIVE

This study aimed to identify the prevalence of and health factors associated with depressive symptoms in older adults with DM.

METHODS

Study design and setting

This cross-sectional study was conducted among 236 older adults enrolled and registered in the Monitoring and Control Service of Hypertension and Diabetes at four Basic Healthcare Units (BHU) in the city of Jequié, in the southwest region of the State of Bahia, Brazil. The estimated population of Jequié is 156,277, with approximately 17,000 older adults aged 60 years or older. Among them, more than 10,000 were assisted under the BHU, and the remaining older adults were distributed between family health strategy units and private healthcare.[21]

Sample

To compose the sample, the E-SUS Component Individual Care Form was used to group individuals with diabetes aged 60 years or older. This is an online registration form that contains patients' personal information regarding their health problems/conditions and is acquired during individual consultations with primary care professionals. After grouping, a sample of 813 individuals was identified. Adopting a 95% confidence level, 5% error, factor prevalence (i.e., depressive symptomatology) of 30.0 %,[22] and 20% loss replacement rate, a sample of 236 individuals was calculated.

The research was conducted in four BHU areas, containing a total of 91 micro-areas. We conducted a simple random draw from the micro-areas, and the respective community health agent was recruited to help during the home visits and assist the research team in locating the residences. In case of the unavailability or absence of older adults with diabetes in the micro-area, the next micro-area was selected, following the survey for older adults with diabetes until saturation was reached for the number of individuals by BHU.

Inclusion criteria were older adults with DM type 2, aged 60 years or older, and who were enrolled in the BHU area and registered in the Monitoring and Control Service of Hypertension and Diabetes. Exclusion criteria were older adults with cognitive difficulties as established by the Mini-Mental State Examination.

Data collection

For data collection, a form comprising two survey sets was applied, including sociodemographic, behavioral, and health conditions, along with the Geriatric Depression Scale (GDS-15).

Dependent variable

For analysis, depressive symptoms were used as the dependent variable. The Brazilian version of the GDS, abbreviated to 15 items, was used in this study. Regarding the definition of depressive symptoms, scores of ≤ 5 points = negative (absence of depressive symptoms) and ≥ 6 points = positive (presence of depressive symptoms).[23]

Independent variables

The sociodemographic variables collected were sex (male and female); age in years tabulated in age groups (60–69, 70–79, and 80 years or older); ethnicity (white, brown, black, and others); marital status (with partner, without partner); and education level divided into two groups (elementary school and above, primary school and below).

The behavioral variables collected were physical activity (yes or no); smoking habits (never smoked, former smoker, and smoker); alcohol habits (non, moderate, excessive consumer); practicing any religion (Catholic, Protestant, and not practicing); and financial difficulty (yes or no).

The health conditions were assessed dichotomously (yes or no), pertaining to family history of diabetes; diabetes complications; rheumatism; osteoporosis; systemic hypertension; circulation problems; heart problems; difficulty sleeping; vision problems; chronic pain; type of DM complications (renal, ocular, circulatory, diabetic foot, and amputation); and prescribed treatment (oral, insulin, non-medicated, none).

Data analysis

Descriptive analysis of population characteristics was performed for all continuous variables (described as mean and standard deviation values) and categorical variables (presented as absolute numbers and percentages). We conducted Chi-square and Fisher's exact tests for categorical variables and Student's t-test for continuous variables. IBM SPSS for Windows statistical package, version 22.0, was used for data analysis (SPSS, Inc., Chicago, Illinois,

United States). To test the hypothesis that a significant proportion of depressive symptoms are related to health factors in older adults with DM, the association between depressive symptoms and the possible risk factors among individuals with DM was assessed using Pearson's chi-square test in bivariate analysis. The independent variables with $P < 0.2$ in the bivariate analysis were entered into a binary logistic regression model using the stepwise regression method. The calculation of the odds ratio (OR) and statistically significant differences ($P < 0.05$) were considered in the absence of overlapping 95% confidence interval (CI) for all analyses.

Ethical considerations

The study was approved by the Research Ethics Committee of the Ana Nery Hospital, under protocol number 1.953.841, on March 8, 2017, and adhered to the Helsinki guidelines at all times. All participants signed an informed consent form before participating in the study.

RESULTS

The final sample comprised 236 older adults with DM. Most were female (76.7%). The mean age was 71.6 years (± 8.03). Of the sample, 64.0% declared brown ethnicity, 81.4% did not have a partner, and 61.9% received primary or lower education.

Depressive symptoms were reported in 24.2% of older adults with DM. **Table 1** shows the characteristics of the study population according to depressive symptoms. Being female without a partner was predominant, although it was not significantly associated with depressive symptoms. Brown ethnicity among older adults was primarily associated with depressive symptoms.

Table 2 presents the behavioral characteristics of the study population. Only alcohol consumption was associated with depressive symptoms.

Table 3 shows the characteristics of the population's health conditions. The existence of any diabetes complications and ocular and circulatory types of DM complications were significantly associated with depressive symptoms. Among comorbidities, rheumatism, osteoporosis, and heart and circulation problems were associated with depressive symptoms. Difficulty sleeping and severe chronic pain were predominant among those with depressive symptoms and were significantly associated with depressive symptoms. The final multivariate analysis model is presented in **Figure 1**, which shows the 95% confidence indices of each variable that remained in the model as well as the OR. Notably, the 95% CI coefficients were attenuated; however, DM complication along with osteoporosis remained associated with depressive symptoms.

DISCUSSION

This study identified a 24.2% prevalence of depressive symptoms in older adults with diabetes and demonstrated a significant association between DM complications and osteoporosis as a health comorbidity.

Studies conducted among older adults in Brazil have shown a prevalence of depressive symptoms ranging from 13% to 39% among community-dwelling older adults. In the present study, the prevalence of depressive symptoms among older adults with DM was 24.2%, which is within the Brazilian average range. Studies reported a 30% and 34.4% prevalence of depressive symptoms in older adults enrolled in the Hiperdia program[22] and those assisted

Table 1. Distribution and association of sociodemographic characteristics of older adults with diabetes mellitus according to depressive symptoms

	Depressive symptoms		P value
	No [n (%)]	Yes [n (%)]	
Sex			
Female	132 (73.7)	49 (86.0)	0.057
Male	47 (26.3)	8 (14.0)	
Ethnicity			
Brown	117 (34.0)	34 (59.6)	
Black	34 (19.0)	9 (15.8)	0.037*
White	28 (15.6)	11 (19.3)	
Other	0 (0.0)	3 (5.3)	
Marital status			
Without partner	144 (80.4)	48 (84.2)	0.525
With partner	35 (19.6)	9 (15.8)	
Education level			
≥ Elementary school	72 (40.2)	18 (31.6)	0.242
≤ Primary education	107 (59.8)	39 (68.4)	

*P < 0.05.

Table 2. Distribution and association of behavioral characteristics of older adults with diabetes mellitus according to depressive symptoms

	Depressive symptoms		P value
	No [n (%)]	Yes [n (%)]	
Religion			
Catholic	70 (39.1)	18 (31.6)	
Protestant	80 (44.7)	22 (38.6)	0.076
Not practicing	29 (16.2)	17 (29.8)	
Financial difficulty			
Yes	82 (45.8)	21 (36.8)	0.234
No	97 (54.2)	36 (63.2)	
Physical activity			
Yes	52 (29.1)	13 (22.8)	0.358
No	127 (70.9)	44 (77.2)	
Smoking			
Smoker	6 (3.4)	8 (8.8)	
Former smoker	68 (38.0)	24 (42.1)	0.164
Never smoked	105 (58.7)	28 (49.1)	
Alcohol consumption			
Excessive	2 (1.1)	4 (7.0)	
Moderate	13 (7.3)	2 (3.5)	0.032*
Non-consumer	164 (91.6)	51 (89.5)	

*P < 0.05.

by the Family Health Strategy, respectively.[24] Both studies were conducted in primary care and used the GDS-15 to investigate the prevalence of depressive symptoms. This shows that the prevalence rates of depressive symptoms among older adults with DM are significantly higher than in those without any chronic disease. Importantly, this can lead to debilitating conditions because of poor metabolic control and the emergence of other health complications resulting from the absence or decrease of treatment adherence, decreased social bonds, and inadequate diet. These negative outcomes have been consistently observed in the relationship between depressive symptoms and poorer self-care among older adults with diabetes, and could be explained by difficulties in maintaining proactive and effective self-care behaviors.[25,26] In the present study, older adults with DM complications were more susceptible to developing depressive symptoms than those without complications. Diabetes complications and depression are reportedly a bi-directional relationship, and the risk of depression is higher in people with diabetes complications, and vice versa.[27] Meta-analysis studies indicate that diabetes increases the risk of developing depression by approximately 25%.[28,29] Moreover, the risk of complications is higher when both diabetes and depression are present. Individuals with DM have a 36% higher risk of developing microvascular complications, such as nephropathy, retinopathy, and neuropathy. Researchers observed a 25% increase in the risk of developing macrovascular complications, such as peripheral vascular disease, erectile dysfunction, and coronary artery disease.[30-32] As noted, there is strong evidence that these comorbidities are linked with disability and loss of years of life.[33] Notably, people with diabetes and symptoms of depression have higher levels of diastolic blood pressure, triglycerides, glycated hemoglobin, higher body mass index, and worse glycemic control. Therefore, older adults are considered at risk for DM complications and other comorbidities that can significantly compromise their health and quality of life.[19,20] Moreover, depressive symptoms may appear even before the diagnosis of DM or during the onset of complications, depending on the individual or the course of the disease.[34,35]

Table 3. Distribution and association of health conditions of older adults with diabetes mellitus according to depressive symptoms

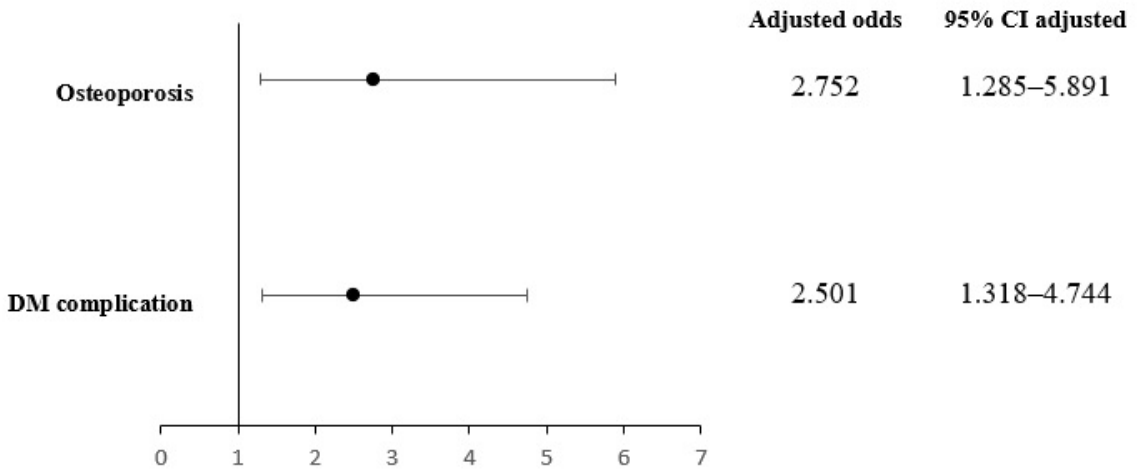
	Depressive symptoms		P value
	No [n (%)]	Yes [n (%)]	
DM family history			
Yes	80 (59.8)	38 (66.7)	
No	11 (6.1)	4 (7.0)	0.550
Do not know	61 (34.1)	15 (26.3)	
Treatment			
Oral	156 (77.2)	53 (79.1)	0.228
Insulin	32 (15.8)	11 (16.4)	0.809
Non-medicated	3 (1.5)	0 (0.0)	0.325
None	11 (5.5)	3 (4,5)	0.806
DM complication			
Yes	69 (38.5)	34 (59.6)	0.005*
No	110 (61.5)	23 (40.4)	
Complication type			
Renal	7 (7.5)	4 (7.4)	0.333
Ocular	31 (33.0)	26 (48.1)	0.000*
Circulatory	42 (44.7)	21 (38.9)	0.047*
Diabetic foot	10 (10.6)	2 (3.7)	0.534
Amputation	4 (4.2)	1 (1.9)	0.826
Rheumatism			
Yes	50 (27.9)	29 (50.9)	0.001*
No	129 (72.1)	28 (49.1)	
Osteoporosis			
Yes	26 (14.5)	20 (35.1)	0.001*
No	153 (85.5)	37 (64.9)	
Hypertension			
Yes	146 (81.6)	49 (86.0)	0.445
No	33 (18.4)	8 (14.0)	
Circulation problems			
Yes	76 (42.5)	35 (61.4)	0.013*
No	103 (57.5)	22 (38)	
Heart problems			
Yes	33 (18.4)	19 (33.3)	0.018*
No	146 (81.6)	38 (66.7)	
Difficulty sleeping			
Yes	82 (45.8)	37 (64.9)	0.012*
No	97 (54.2)	20 (35.1)	
Vision problems			
Yes	80 (44.7)	32 (56.1)	0.132
No	99 (55.3)	25 (43.9)	
Chronic pain			
Yes	81 (45.3)	44 (77.2)	0.000*
No	98 (54.7)	13 (22.8)	

*P < 0.05; DM = diabetes mellitus.

Among the health comorbidities evaluated in this study, osteoporosis remained in the final model even after adjustment, showing an increased risk for depressive symptoms in older adults with DM. This comorbidity is predominantly cited by older adults in aging studies,[7,36] including being associated with diabetes itself.[37,38]

The presence of osteoporosis combined with connective tissue problems, neuropathies, and vasculopathies may increase the incidence of complications in older adults with diabetes. This further contributes to their limitations and restricted autonomy, functional disability, fragility, and the potential development of depressive symptoms.[39,40]

Osteoporosis commonly causes pain, which directly affects the quality of life of older adults with diabetes. Furthermore, complementary data in this study showed that 77.2% of older adults with depressive symptoms had self-reported chronic pain. Whether this pain is linked to musculoskeletal pain or complications of DM, it remains a primary reason for older adults to seek health services.[37,41,42] Thus, this study expands the knowledge that the presence of osteoporosis and diabetes complications in older adults can be associated with depressive symptoms. Moreover, when



DM = diabetes mellitus.

Figure 1. Odds ratio and 95% confidence interval (CI) of final regression model for risk of depressive symptoms.

older adults seek health services, health professionals must critically examine these associations and employ a holistic approach, for example, by testing for depressive symptoms.

In this context, testing for depressive symptoms in individuals with diabetes to enable early detection and treatment is one of the challenges faced by primary healthcare professionals. Lack of screening may be attributed to absent or limited training in mental health issues, inability or lack of skills to use mental health assessments, and difficulties in distinguishing depression symptoms or diabetes complications from symptoms of physical illness. Ideally, patients with diabetes should be referred to mental health consultations and supported in self-management education, which can provide them with an increased ability to maintain their treatments and identify coping strategies for depressive symptoms.[43,44]

CONCLUSION

The present study findings are broadly consistent with data from national and international literature, showing a significant prevalence of depressive symptoms in older adults with type 2 DM. In conclusion, this study provides strong evidence that complications of DM significantly increase the risk of depressive symptoms in older adults, especially those with DM and osteoporosis. This perspective suggests that, by identifying groups at greater risk, primary care professionals can develop care strategies and refer older adults with DM for a mental health consultation to reduce complications and improve prognosis. In the present study, individuals with DM at a higher risk for the development of depressive symptoms were represented among those with complications arising from DM and musculoskeletal comorbidities, such as osteoporosis.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edition. Brussels, Belgium: 2021. Available from: https://diabetesatlas.org/. Accessed in 2022 (May 31).
2. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes 2019-2020. São Paulo: Clannad; 2020:419. Available from: http://www.saude.ba.gov.br/wp-content/uploads/2020/02/Diretrizes-Sociedade-Brasileira-de-Diabetes-2019-2020.pdf. Accessed in 2022 (May 31).
3. Barcelos-Ferreira R, Izbicki R, Steffens DC, Bottino CM. Depressive morbidity and gender in community-dwelling Brazilian elderly: Systematic review and meta-analysis. Int Psychogeriatr. 2010;22(5):712-26. PMID: 20478096; https://doi.org/10.1017/S1041610210000463.
4. Souza A, Sena E, Meira E, Silva D, Alves M, Pereira L. Perfil sociodemográfico e de saúde de idosos com sintomas depressivos [Sociodemographic and health profile of elderly patients with depressive symptoms]. UERJ Nursing Journal. 2013;21(3):355-60. Available from: https://www.e-publicacoes.uerj.br/index.php/enfermagemuerj/article/view/7523. Accessed in 2022 (May 31).
5. Büchtemann D, Luppa M, Bramesfeld A, Riedel-Heller S. Incidence of late-life depression: a systematic review. J Affect Disord. 2012;142(1-3):172-9. PMID: 22940498; https://doi.org/10.1016/j.jad.2012.05.010.
6. Madeira TCS, Aguiar MIF, Bernardes ACF, et al. Depressão em idosos hipertensos e diabéticos no contexto da atenção primária em saúde [Depression in elderly hypertensive and diabetic patients in the context of primary health care]. Rev APS. 2013;16(4):393-8. Available from: https://aps.ufjf.emnuvens.com.br/aps/article/view/1895/762. Accessed in 2022 (May 30).

7. Ramos GCF, Carneiro JA, Barbosa ATF, Mendonça JMG, Caldeira AP. Prevalência de sintomas depressivos e fatores associados em idosos no norte de Minas Gerais: Um estudo de base populacional [Prevalence of depressive symptoms and associated factors among elderly in northern Minas Gerais: a population-based study]. J Bras Psiquiatr. 2015;64(2):122-31. https://doi.org/10.1590/0047-2085000000067.
8. Peltzer K, Phaswana-Mafuya N. Depression and associated factors in older adults in South Africa. Glob Health Action. 2013;6:1-9. PMID: 23336621; https://doi.org/10.3402/gha.v6i0.18871.
9. Mushtaque A, Gulati R, Hossain MM, Azmi SA. Prevalence of depression in patients of type 2 diabetes mellitus: A cross sectional study in a tertiary care centre. Diabetes Metab Syndr. 2016;10(4):238-41. PMID: 27484439; https://doi.org/10.1016/j.dsx.2016.06.016.
10. Golden SH, Shah N, Naqibuddin M, et al. The Prevalence and Specificity of Depression Diagnosis in a Clinic-Based Population of Adults with Type 2 Diabetes Mellitus. Psychosomatics. 2017;58(1):28-37. PMID: 27692654; https://doi.org/10.1016/j.psym.2016.08.003.
11. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol. 2015;3(6):461-71. PMID: 25995124; https://doi.org/10.1016/S2213-8587(15)00134-5.
12. Bădescu SV, Tătaru C, Kobylinska L, et al. The association between Diabetes mellitus and Depression. J Med Life. 2016;9(2):120-5. PMID: 27453739.
13. Anwar N, Kuppili PP, Balhara YPS. Depression and physical noncommunicable diseases: The need for an integrated approach. WHO South East Asia J Public Health. 2017;6(1):12-7. PMID: 28597853; https://doi.org/10.4103/2224-3151.206158.
14. Barreto Andrade DM, Montargil Rocha R, Santos Ribeiro IJ. Depressive Symptoms and Family Functionality in the Elderly with Diabetes Mellitus. Issues Ment Health Nurs. 2020;41(1):54-8. PMID: 31545908; https://doi.org/10.1080/01612840.2019.1636167.
15. Massey CN, Feig EH, Duque-Serrano L, Huffman JC. Psychological Well-Being and Type 2 Diabetes. Curr Res Diabetes Obes J. 2017;4(4):555641. PMID: 29276801; https://doi.org/10.19080/crdoj.2017.04.555641.
16. Holt RI, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep. 2014;14(6):491. PMID: 24743941; https://doi.org/10.1007/s11892-014-0491-3.
17. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1603-58. Erratum in: Lancet. 2017;389(10064):e1. PMID: 27733283; https://doi.org/10.1016/S0140-6736(16)31460-X.
18. Novak M, Mucsi I, Rhee CM, et al. Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients with Diabetes with Comorbid Depression. Diabetes Care. 2016;39(11):1940-7. PMID: 27311494; https://doi.org/10.2337/dc16-0048.
19. Wang B, Yuan J, Yao Q, et al. Prevalence and independent risk factors of depression in Chinese patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2016;4:S36. https://doi.org/10.1016/S2213-8587(16)30391-6.
20. Zhang W, Xu H, Zhao S, et al. Prevalence and influencing factors of co-morbid depression in patients with type 2 diabetes mellitus: a General Hospital based study. Diabetol Metab Syndr. 2015;7:60. PMID: 26167205; https://doi.org/10.1186/s13098-015-0053-0.
21. Instituto Brasileiro de Geografia e Estatística. Projeções da População | IBGE. Portal IBGE, 2018. Available from: https://www.ibge.gov.br/estatisticas/sociais/populacao/9109-projecao-da-populacao.html?=&t=o-que-e. Accessed in 2022 (Jul 19).
22. Sass A, Gravena AAF, Pilger C, Freitas Mathias TA, Marcon SS. Depressão em idosos inscritos no Programa de Controle de hipertensão arterial e diabetes mellitus. ACTA Paul Enferm. 2012;25(1):80-5. https://doi.org/10.1590/S0103-21002012000100014.
23. Almeida OP, Almeida SA. Reliability of the Brazilian version of the geriatric depression scale (GDS) short form. Arq Neuropsiquiatr. 1999;57(2B):421-6. PMID: 10450349; https://doi.org/10.1590/S0004-282X1999000300013.
24. Alvarenga MRM, Oliveira MAC, Faccenda O. Sintomas depressivos em idosos: análise dos itens da Escala de Depressão Geriátrica. ACTA Paul Enferm. 2012;25(4):497-503. Available from: https://doi.org/10.1590/S0103-21002012000400003.
25. Egede LE, Ellis C. Diabetes and depression: global perspectives. Diabetes Res Clin Pract. 2010;87(3):302-12. PMID: 20181405; https://doi.org/10.1016/j.diabres.2010.01.024.
26. Gonzales JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care. 2008;31(12):2398-403. PMID: 19033420; https://doi.org/10.2337/dc08-1341.
27. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med. 2001;63(4):619-30. PMID: 11485116; https://doi.org/10.1097/00006842-200107000-00015.
28. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA. 2008;299(23):2751-9. PMID: 18560002; https://doi.org/10.1001/jama.299.23.2751.
29. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia. 2010;53(12):2480-6. PMID: 20711716; https://doi.org/10.1007/s00125-010-1874-x.
30. Michels MJ. Depressão em diabéticos tipo 2: prevalência, fatores associados, avaliação da aderência ao tratamento e complicações do diabetes. Universidade Federal de Santa Catarina. 2010;1-76. Available from: https://repositorio.ufsc.br/xmlui/handle/123456789/94613?show=full. Accessed in 2021 (Dec 22).
31. van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS One. 2013;8(3):e57058. PMID: 23472075; https://doi.org/10.1371/journal.pone.0057058.
32. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15-S33. Erratum in: Diabetes Care. 2021;44(9):2182. PMID: 33298413; https://doi.org/10.2337/dc21-S002.

33. Sartorius N. Depression and diabetes. Dialogues Clin Neurosci. 2018;20(1):47-52. PMID: 29946211; https://doi.org/10.31887/DCNS.2018.20.1/nsartorius.
34. Kan C, Silva N, Golden SH, et al. A Systematic Review and Meta-analysis of the Association Between Depression and Insulin Resistance. Diabetes Care. 2013;36(2):480-9. PMID: 23349152; https://doi.org/10.2337/dc12-1442.
35. Braga DC, Carli FKF, Nyland LP, Bonamigo EL, Bortolini SM. Fatores associados à depressão em indivíduos com diabetes mellitus. Arq Catarinenses Med. 2017;46(3):118-28. Available from: http://www.acm.org.br/acm/seer/index.php/arquivos/article/view/313/180. Accessed in 2021 (Dec 22).
36. Gonçalves VC, Andrade KL. Prevalência de depressão em idosos atendidos em ambulatório de geriatria da região nordeste do Brasil (São Luís-MA) [Prevalence of depression in elderly assisted in a geriatrics ambulatory in northeastern Brazil (São Luis city, state of Maranhão)]. Rev Bras Geriatr Gerontol. 2010;13(2):289-99. https://doi.org/10.1590/S1809-98232010000200013.
37. Serban AL, Udrea GF. Rheumatic manifestations in diabetic patients. J Med Life. 2012;5(3):252-7. PMID: 23049626.
38. Chen HL, Deng LL, Li JF. Prevalence of Osteoporosis and Its Associated Factors among Older Men with Type 2 Diabetes. Int J Endocrinol. 2013;2013:285729. PMID: 23401682; https://doi.org/10.1155/2013/285729.
39. Pinto-Junior EP, Nogueira FP, Valença TDC, Almeida V. Doenças reumáticas e incapacidades no contexto do envelhecimento populacional. Rev Bras Cien Envelhec Hum. 2010;7(3). Available from: http://seer.upf.br/index.php/rbceh/article/view/829. Accessed in 2021 (Dec 22).
40. Linhares BN, Naves VN, Matias RN, Oliveira JCP, Silva DOF. A correlação entre Depressão e Diabetes Mellitus tipo 2 [The correlation between depression and type 2 diabetes]. Rev Med Saude Brasilia. 2015;4(3):341-9. Available from: https://portalrevistas.ucb.br/index.php/rmsbr/article/view/6133/4114. Accessed in 2021 (Dec 22).
41. Rosa MR, Patrício ZM, Silvério MR, Rumel D. Reasons that made aged people seek care at a basic health unit Rev Lat Am Enfermagem. 2009;17(5):670-6. PMID: 19967216; https://doi.org/10.1590/s0104-11692009000500012.
42. Dellaroza MS, Pimenta CA, Duarte YA, Lebrão ML. Dor crônica em idosos residentes em São Paulo, Brasil: prevalência, características e associação com capacidade funcional e mobilidade (Estudo SABE) [Chronic pain among elderly residents in São Paulo, Brazil: prevalence, characteristics, and association with functional capacity and mobility (SABE Study)]. Cad Saude Publica. 2013;29(2):325-34. PMID: 23459818; https://doi.org/10.1590/S0102-311X2013000200019.
43. Owens-Gary MD, Zhang X, Jawanda S, et al. The Importance of Addressing Depression and Diabetes Distress in Adults with Type 2 Diabetes. J Gen Intern Med. 2019;34(2):320-4. PMID: 30350030; https://doi.org/10.1007/s11606-018-4705-2.
44. Powers MA, Bardsley J, Cypress M, et al. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. Diabetes Care. 2015;38(7):1372-82. PMID: 26048904; https://doi.org/10.2337/dc15-0730.

Authors' contributions: Andrade DMB: conceptualization (lead), data curation (lead), formal analysis (equal), investigation (lead), methodology (equal), project administration (lead), resources (equal), software (supporting), supervision (equal), validation (equal), visualization (equal), writing-original draft (lead) and writing-review and editing; Rocha RM: conceptualization (supporting), data curation (equal), funding acquisition (supporting), investigation (supporting), methodology (supporting), project administration (lead), resources (equal), supervision (lead), validation (equal), visualization (equal) and writing-review and editing (equal); and Ribeiro IJS: conceptualization (supporting), data curation (supporting), formal analysis (lead), methodology (supporting), software (lead), supervision (equal), validation (equal), visualization (equal) and writing-review and editing (equal). All authors actively contributed to the discussion of the study results and reviewed and approved the final version of the manuscript

Sources of funding: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – finance code 001

Conflicts of interest: The authors declare no conflicts of interest

Date of first submission: September 17, 2021
Last received: July 11, 2022
Accepted: August 9, 2022

Address for correspondence:
Diego Micael Barreto Andrade
Faculty of Health Sciences, Doctoral School of Health Sciences, University of Pécs (UP), Pécs, Vörösmarty Mihály Street 4, 7621, Hungary
Tel. (+36) 30 6804012
E-mail: andrade.diego@etk.pte.hu

Translation, Validity and Internal Consistency of the Quality of Dying and Death Questionnaire for Brazilian families of patients that died from cancer: a cross-sectional and methodological study

Bianca Sakamoto Ribeiro Paiva[I], Talita Caroline de Oliveira Valentino[II], Mirella Mingardi[III], Marco Antonio de Oliveira[IV], Julia Onishi Franco[V], Michelle Couto Salerno[VI], Helena Palocci[VII], Tais Cruz de Melo[VIII], Carlos Eduardo Paiva[IX]

Hospital de Câncer de Barretos, Barretos (SP), Brazil

[I]PhD. Researcher and Professor, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0002-2711-8346

[II]MSc. Nurse and Doctoral Student, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0001-7565-4437

[III]RN. Nurse and Master's Student, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0001-9012-0601

[IV]MSc. Biostatistics, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0001-6879-2778

[V]MD. Physician, Dr. Paulo Prata, School of Health Sciences of Barretos and Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0002-1001-4970

[VI]RN. Research Nurse, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0002-8138-7678

[VII]MD. Physician, Dr. Paulo Prata, School of Health Sciences of Barretos and Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0002-4486-2118

[VIII]MD. Physician, Dr. Paulo Prata, School of Health Sciences of Barretos and Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0001-6907-142X

[IX]PhD. Physician and Professor, Palliative Care and Quality of Life Research Group (GPQual), Postgraduate Program, Hospital de Câncer de Barretos, Barretos (SP), Brazil.
https://orcid.org/0000-0002-7934-1451

KEY WORDS (MeSH terms):
Validation study.
Neoplasms.
Death.

AUTHORS' KEY WORDS:
The quality of dying and death.
Cancer.
Questionnaire.

ABSTRACT

BACKGROUND: The Quality of Dying and Death Questionnaire (QoDD) may prove to be an important evaluation tool in the Brazilian context, and, therefore, can contribute to a more precise evaluation of the dying and death process, improving and guiding the end-of-life patient care.

OBJECTIVE: To translate and cross-culturally adapt the QoDD into Brazilian Portuguese and measure its validity (convergent and known-groups) and internal consistency

DESIGN AND SETTING: A cross-sectional, methodological study was conducted at the Hospital de Câncer de Barretos, Brazil

METHODS: A total of 78 family caregivers participated in this study. Semantic, cultural, and conceptual equivalences were evaluated using the content validity index. The construct validity was assessed through convergent validation and known groups analysis [presence of family members at the place of death; feel at peace with dying; and place of death (hospital versus home; hospital versus Palliative Care)]. Internal consistency was evaluated using Cronbach's alpha.

RESULTS: The questionnaire was translated into Brazilian Portuguese and presented evidence of a clear understanding of its content. Cronbach's alpha values were ≥ 0.70, except for the domains of treatment preference (α = 0.686) and general concerns (α = 0.599). The convergent validity confirmed a part of the previously hypothesized correlations between the Palliative Care Outcome Scale-Brazil (POS-Br) total scores and the QoDD domain scores. The QoDD-Br domains could distinguish the patients who died in palliative care and general wards.

CONCLUSION: The QoDD-Br is a culturally adapted valid instrument, and may be used to assess the quality of death of cancer patients.

INTRODUCTION

The death process is subjectively determined and may be influenced by cultural factors, individual judgments, type and stage of the underlying disease, and the social and professional role with respect to the death experience.[1] The interest in promoting a "good death" has been increasingly discussed, mainly due to the increase in life expectancy of the population and advances in medicine.[1] The Institute of Medicine Committee on Care at the End of Life characterized high-quality death as "death free from avoidable anguish and suffering for patients, families and their caregivers, according to the wishes of patients and caregivers and in line with clinical, cultural and ethical standards."[2,3] The end-of-life stage leads to changes, which allows the development of standards that improve the quality of death (QOD). Simultaneously, a "good death" is equivalent to a death consistent with the patient's personality[4] and autonomy.

Therefore, QOD may be defined as the assessment of the last days of life and the moment of death, respecting the way that moment is prepared, faced, experienced and dealt with by those who have known terminal illness.[5] Different authors provide varied criteria for determining the QOD, such as reaffirming the need to prioritize the absence of pain during the end-of-life period. However, there is a consensus that the quality of death and dying is greater than the control of physical symptoms (such as pain), since there are multiple dimensions inherent to this process.[6-9]

Therefore, practical measures are necessary to improve this indicator in the Brazilian context.

Among all the instruments of the QOD assessment described in the literature, the "Quality of Dying and Death Questionnaire" (QoDD) is the most widely studied and best validated.[1,10,11] It was developed by Patrick et al.[4] due to a shortage of instruments for assessing the QOD. The study expected to provide a better evaluation of post death reports and the experience regarding the QOD and dying, as well as to evaluate the interventions that improve the quality of care at the end of life.

The QoDD has been adapted in different languages and cultures and has demonstrated greater validity and reliability than other questionnaires.[11,12] It presents satisfactory psychometric results, with an internal consistency of 0.88 and test-retest reliability of 0.7 in studies conducted in Germany and Spain.[3,13] However, no Portuguese version has been culturally adapted and validated in the Brazilian population. The QoDD may prove to be an important evaluation tool in the Brazilian context, and thus, may contribute to a more precise evaluation of the dying and death process, improving and guiding the end-of-life patient care.

OBJECTIVE

The purpose of this study was to translate and cross-culturally adapt the QoDD into Brazilian Portuguese and measure its validity (convergent and known-groups) and internal consistency.

METHODS

Study design

This was a descriptive, cross-sectional, and methodological study.

Setting

The study was conducted at Hospital do Câncer de Barretos (Barretos, São Paulo, Brazil), a reference hospital in Latin America for cancer treatment. It is an assistential, teaching, and research institution.

Patient and public involvement statement

Caregivers (family members) were not involved in the design or planning of the study; however, were informed regarding the nature and purpose of this study. Authorization for participation was obtained in the form of signed consent forms from the primary family caregiver. The entire validation process was performed following the permission of one of the authors of the original QoDD.[10]

Phase I - Translation and cultural adaptation process

The cross-cultural adaptation of the QoDD was initiated after obtaining permission from the author of the original version.[10] International methodology adopted for the translation and cultural adaptation included translation, a synthesis of the translations, back-translation, an expert panel, and a pretest according to the methodology proposed by Beaton et al.[14] and Souza and Rojjanasrirat.[15]

Initially, the original questionnaire was translated from English into Portuguese by two independent translators, both native English speakers, without the knowledge of the issues addressed by the QoDD. The translated versions of the questionnaire were coded as T1 and T2.

The second step included a synthesis meeting of four specialized professionals: a doctor experienced in palliative care (PC), a researcher experienced in the QOD, and two other professionals in the research field experienced in the care practice. In this step, a synthesized version (T12) was generated from the evaluation of T1 and T2 translations. Each aspect of the translations was analyzed and discussed to achieve a consensus between the two versions, ensuring equivalence.

Next, the instrument was back translated from Portuguese into the original language. Two independent translators performed the back-translations (BT1 and BT2), one American with fluency in Portuguese and the other, a native Brazilian with expertise in the English language.

An expert committee meeting was conducted during which all the material produced in the previous steps was analyzed. This team of five experts included a clinical oncologist, a palliative physician, a research nurse in PC, a research psychologist in PC and a biostatistician experienced in the validation of assessment instruments. The committee's main objective was to produce a final version of the tool that would be culturally adapted for use during the pre-testing. To assess the representativeness of each item, a Likert scale with scores between 1 and 4 was used. The content validity index (CVI) was calculated by summing the equivalences of the items and dividing it by the total number of items. A minimum value of 0.80 was accepted for the evaluated item to be considered appropriate.[15]

The pre-testing phase included 26 family caregivers who were >18 years, of either sex, considered the primary caregiver, aware that the patient's death was from cancer, and knew how to read. Family caregivers with significant hearing loss that prevented them from telephonic communication were excluded. The family caregivers were contacted via telephone within 4-12 weeks after the date of death of their loved one.

Figure 1 shows the steps of the translation and cross-cultural adaptation process.

Phase II - Assessment of psychometric properties

A different sample of family caregivers was contacted by phone to measure the psychometric properties of the QoDD-Br. One of the measures of reliability - internal consistency - was assessed using Cronbach's alpha. Values from 0.70-0.95 were considered

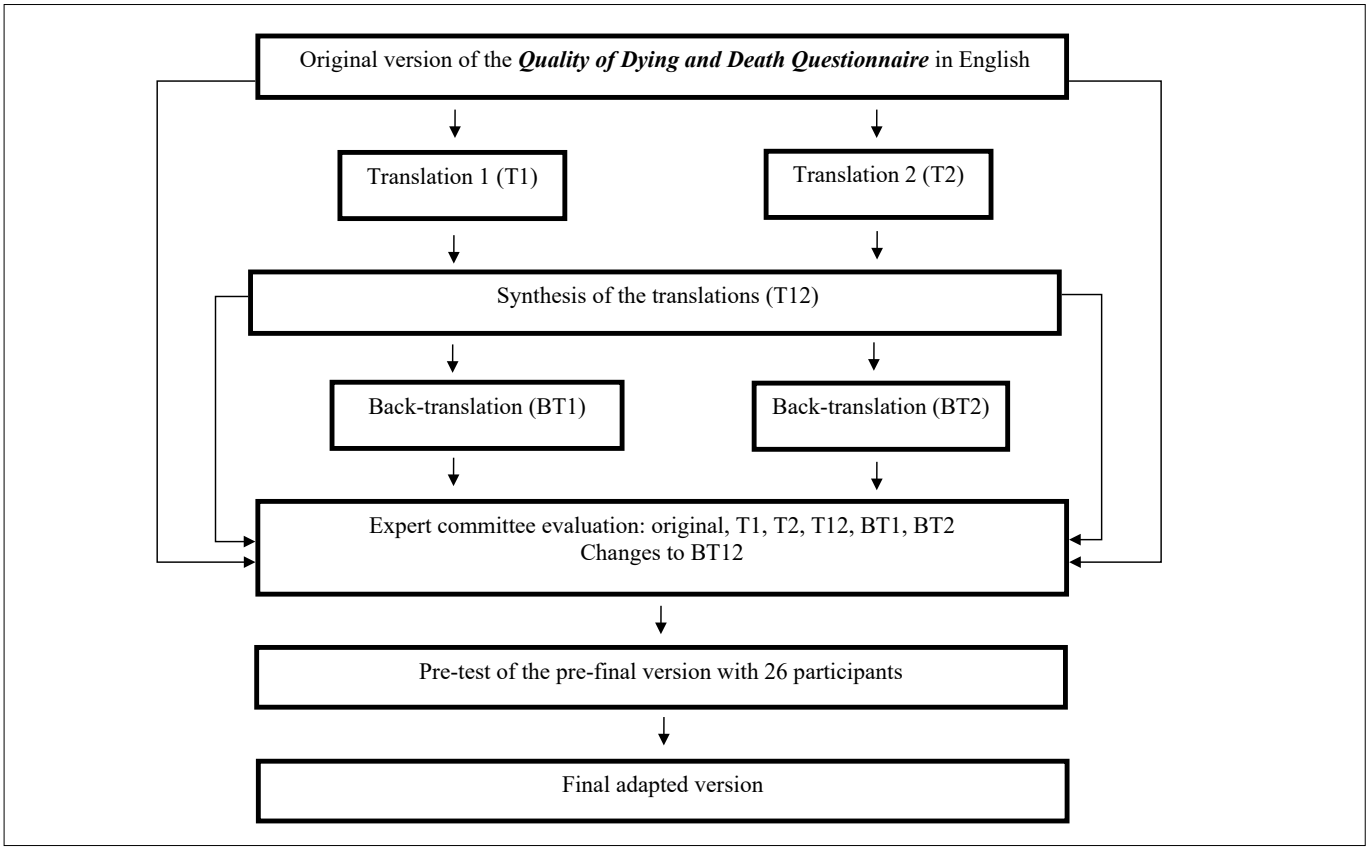


Figure 1. Flowchart of the translation and cross-cultural adaptation steps.

to be adequate.[16] For convergent construct validity, correlations between the QoDD-Br and the Palliative Care Outcome Scale-Brazil (POS-Br; an assessment tool designed to address multidimensional aspects of palliative care, such as physical and psychological symptoms, spiritual considerations, practical concerns, and emotional and psychosocial needs)[17,18] scores were hypothesized a priori by the researcher's judgment based on a clinical routine and the literature. Correlations with values ≥ 0.4 (moderate to highly strong) were considered acceptable.[19,20] In the known-groups analysis, the groups were compared using the mean (standard deviation) of each domain, as measured by the QoDD-Br, to assess whether the instrument could discriminate between the groups as hypothesized.

Primary family caregivers of patients who died from cancer and were > 18 years of age were invited to participate in the study's validation step. They were selected through telephone contact, and they consented to answer the QoDD-Br questionnaire adapted to the Brazilian culture and the POS-Br. To preserve their mental health and avoid the worsening of their psychological condition due to participation in the study, the Patient Health Questionnaire-9 (PHQ-9)[21] was administered to screen for depressive symptoms and suicide risk. Family caregivers who selected option 1 - several days, 2 - more than half the days or 3 - almost every day in question 9 of the PHQ-9 questionnaire (suicidal ideation) or had a total score ≥ 12, were excluded.[22]

Instruments

Quality of Dying and Death Questionnaire (QoDD)

It comprised 31 items divided into six domains measuring aspects related to symptoms and personal control, preparation for death, family concerns, treatment preferences, whole person concerns, and moment of death. It takes into account the experiences in the last seven days of the patient's life and the state of the patient. The response scale used is a Likert-type scale with scores varying from 0 to 100, where higher scores indicate better QOD.[10]

Palliative Care Outcome Scale - Brazil (POS-Br)

The POS-Br is a tool largely used to measure the quality of life (QOL) during the last 3 days of the patient's life,[20] as well as of patients who undergo PC. This scale consists of 11 items. The answers are provided on a five-point Likert scale, except item 9, which has three points, and an open question regarding the main problems experienced by the patient. The POS-Br scores

range from 0 to 40 points, with 0 representing the best QOL and 40 representing the worst QOL.[17,18]

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a useful tool for the screening of depressive symptoms. It includes nine questions, rated on a four-point Likert scale (0 to 3), for a possible total of 27 points. The final score classification is as follows: 0–4, without depression; 5–9, mild depression; 10–14, moderate depression; 15–19, moderate to severe depression; and > 20, severe depression.[21]

Calculation of sample size

Sample calculation for the pretest phase followed the methodology described by Beaton et al., which advocates the participation of 10–40 participants.[14] In this study's pre-testing phase, 33 individuals participated. For construct validity, the sample size calculation was a minimum of 50 patients.[16]

Statistical analyses

Internal consistency was assessed using Cronbach's alpha coefficient, and a value between 0.70 and 0.95 was considered adequate.[16] Convergent validity correlations were measured using Pearson's correlation coefficient ($r > 0.4$).[19] The calculation was performed considering total scores on the QoDD-Br and POS-Br instruments and subsequently the scores in their domains. For the known-groups analysis, the groups were compared using the nonparametric Mann–Whitney U test. It was expected that the QoDD-Br would discriminate between the caregiving groups in accordance with the hypotheses based on the following factors: presence of family members at the place of death (yes versus no); feel at peace with dying (yes versus no); and place of death (hospital versus home; hospital versus PC hospital).

The data were stored on the REDCap Plataform[23] and evaluated using the IBM-SPSS software, version 21.0 (IBM Corp., Armonk, New York, United States). The significance level was set at 0.05.

Ethical aspects

The study was approved by the Committee of Ethics in Research of Hospital de Câncer de Barretos, under opinion n. 1329/2017 (May 18, 2017). All the participants invited to participate in the study signed the free and informed consent form.

RESULTS

Phase I - Translation and cultural adaptation process translation

The title and 31 items were translated with similar meaning, with no grammatical or semantic distinctions between T1 and T2. The original acronym was maintained, and Br was added to identify the Brazilian instrument: QoDD-Br. The back-translations (BT1 and BT2) did not indicate significant conceptual changes or inconsistencies in the translation process and were useful in guiding effective and consistent actions in the expert committee step.

Table 1 shows the items questioned by the expert committee and their respective equivalences. From the 112 questionnaire items evaluated, there was a 100% agreement on 104 items

Table 1. Description of the items with modifications requested by the expert committee

Items	Statement or question	Equivalences			Total CVI
		Semantic	Cultural	Conceptual	
1	Quality of Dying and Death (QODD) Questionnaire	0.8	1	1	0.93
2	QoDD: Interview following the death of a loved one	0.6	0.6	0.8	0.67
18	7 recall days 7	0.8	1	0.8	0.87
19	30 recall days 30	0.8	1	0.8	0.87
34	Each question has two parts. The first part will ask you how often X experienced each item using a scale where 0 is "none of the time" and 5 is "all of the time"	0.6	1	1	0.87
37	Let us start with an example. In the last month of her/his life, how often did X listen to music? I would like you to use the first scale to tell me how often X listened to music during the last month of her/his life, with 0 being "none of the time" and 5 being "most of the time"	0.8	1	1	0.93
42	How often did X appear to have control over what was going on around her/him?	0.8	1	1	0.93
78	Where did your loved one die?	1	1	0.8	0.93
99	What is the highest school level you completed?	1	0.8	1	0.93

Equivalences calculated by the content validity index (CVI).

classified with scores of 3 and 4; CVI = 1. Items 1, 2, 18, 19, 34, 42, 78 and 99 received a score of 2, and thus, changes suggested by the experts were necessary.

Each interview was conducted over telephone and lasted approximately 30 minutes. The initial sample included 33 participants; two refused to participate due to lack of time, and five were excluded because they reported that they were not prepared to remember the death of their loved ones. The sociodemographic characteristics of the family caregivers and patients are shown in **Table 2**. All the participants answered a questionnaire with questions related to the understanding of each item.

Annex 1 shows the final version of the QoDD-Br to Brazilian culture.

Phase II - Assessment of psychometric properties

A total of 566 family caregivers were screened as potential participants. Of these, only 114 answered the telephone calls during which they were invited to participate in the study. Twelve (10.5%) family caregivers refused to participate in the study and 50 (43.8%) were excluded due to depression symptoms identified by the PHQ-9. Thus, final sample included 52 (45.6%) family caregivers

Among the included family caregivers (n = 50), 41 (78.8%) were women, 25 (48.1%) were married, 18 (34.6%) were children, and 17 (32.7%) were spouses. Regarding the characteristics of the patients, 37 (32.5%) had gastrointestinal cancer, 19 (16.7%) had lung cancer, 10 (8.8%) had head and neck cancer, and 10 (8.8%) had hematological cancer. Seven (13.5%) of the patients died at home.

Regarding internal consistency, most QoDD-Br domains presented Cronbach's α values ≥ 0.70, with the exception of the treatment preference (α = 0.686) and general concerns (α = 0.599) domains (**Table 3**). Regarding convergent validity, the a priori hypothesized correlations were confirmed between the domains "preparation for death" (r = -0.422, P = 0.002), "symptoms and personal control" (r = -0.465, P = 0.001), and "whole person concerns" (r = -0.405, P = 0.003). The correlations between the QoDD-Br and POS-Br scores are summarized in **Table 4**. Researchers expected that the instrument could discriminate the presence of family members at the place of death (yes versus no), feeling at peace with dying (yes versus no), and place of death (hospital versus home; hospital versus PC hospital). The known-groups analysis showed that the instrument could discriminate between the family caregiver groups, as shown in **Table 5**.

Table 2. Sociodemographic characteristics of the participants who completed the pretest

Variable		Family caregivers		Patients	
		n	%	n	%
Sex	Female	22	84.6	14	53.8
	Male	4	15.4	12	46.2
Race	White	16	61.5	20	77.0
	Black	3	11.5	1	3.8
	Mixed	7	27.0	5	19.2
Education	Primary	6	23.0	7	27.0
	Secondary	12	46.0	14	54.0
	Higher	8	31.0	5	19.0
Religion	Catholic	19	73.1	19	73.1
	Evangelical	5	19.2	5	19.2
	Spiritist	2	7.7	2	7.7
Civil Status	Married	14	53.8	15	57.7
	Single	7	27.0	4	15.4
	Widowed	3	11.5	6	23.1
	Separated	2	7.7	1	3.8
Place of death	Acute Care Hospital	-	-	1	3.8
	PC Hospital[1]	-	-	25	96.2
Relatives	Father	1	3.8		
	Mother	1	3.8	-	-
	Son/Daughter	9	35.0	-	-
	Nephew/Niece	2	7.7	-	-
	Son/Daughter -in-law	2	7.7		
	Husband/Wife	6	23.0	-	-
	Others[2]	5	19.0	-	-
Time interval between patient's death and pretest (days)	Mean (SD)	76.12 (27.71)			

SD = standard deviation. [1]PC Hospital: hospital exclusively dedicated to patients in palliative care; [2]Others: Friend, stepdaughter, boyfriend or cousin.

Table 3. Internal consistency of the Quality of Dying and Death Questionnaire-Brazilian (QoDD-Br)

QoDD-Br domains	Cronbach's alpha
Symptoms and personal control	0.825
Preparation for death	0.776
Moment of death	0.814
Family	0.742
Treatment preference	0.686
Overall person concerns	0.599
QoDD-Br total score	0.955

Table 4. Convergent validation (correlations) between the Quality of Dying and Death Questionnaire-Brazilian (QoDD-Br) domains and Palliative Care Outcome Scale-Brazil (POS-Br)

QoDD-Br domains	POS-Br total	P value
Symptoms and personal control	**-0.465**	0.001
Preparation for death	**-0.422**	0.002
Moment of death	-0.358	0.009
Family	-0.125	0.377
Treatment preference	-0.045	0.754
Overall person concerns	**-0.405**	0.003
QoDD-Br total score	-0.242	0.290

Correlation with a coefficient above 0.4.

Table 5. Mean comparison of domains measured by Quality of Dying and Death Questionnaire-Brazilian (QoDD-Br) version between family caregivers' groups (known-groups analysis)

Variables	Category	QoDD-Br Domains												QoDD-Br Total score	
		Symptoms and personal control		Preparation for death		Moment of Death		Family		Treatment preference		Overall person concerns			
		Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P
Presence of family members at the place of death	No	38.57 (13.28)	0.253*	54.68 (17.02)	0.124*	34.76 (30.78)	*0.023*	65.69 (28.06)	0.329	70.24 (25.65)	0.557	58.10 (17.39)	0.098	53.47 (16.10)	0.065*
	Yes	50.72 (27.11)		67.09 (19.81)		71.37 (32.41)		76.36 (23.77)		75.68 (26.68)		70.26 (22.44)		66.77 (17.42)	
Feel at peace with dying	No	41.79 (24.74)	0.180*	56.75 (17.38)	*0.036**	48.33 (34.11)	*0.017*	72.30 (24.15)	0.474	74.05 (28.01)	0.724	58.04 (19.84)	0.005	56.31 (18.39)	*0.013**
	Yes	52.99 (26.39)		69.87 (19.81)		72.35 (33.36)		75.99 (24.28)		78.64 (21.64)		75.20 (20.92)		70.00 (15.66)	
Place of death	Hospital	50.65 (26.11)	0.387	64.83 (20.16)	0.589*	62.63 (35.17)	0.072	74.11 (25.10)	0.678	73.90 (27.64)	0.762	73.93 (13.30)	0.500*	64.40 (18.56)	0.652*
	Home	39.05 (24,03)		69.23 (17.97)		90.95 (11.01)		80.14 (19.72)		81.43 (15.97)		67.80 (23.15)		67.70 (11.96)	
Place of death	PC Hospital	55.16 (27.41)	0.178*	72.83 (19.01)	*0.001*	71.03 (33.24)	0.052	80.16 (22.78)	*0.044*	82.56 (21.93)	*0.017*	75.10 (20.74)	*0.012**	70.32 (17.96)	*0.015**
	Hospital	44.47 (23.52)		53.87 (16.49)		51.14 (35.34)		65.84 (26.35)		61.39 (30.74)		57.81 (23.03)		56.50 (16.71)	

SD = standard deviation. Statistical analyses were performed using nonparametric Mann–Whitney U test. *U-test. Statistically significant P values at the 0.05 level are in italics.

DISCUSSION

This study translated, culturally adapted, and validated the QoDD for use in the Brazilian population.[14,24] The QoDD may prove to be an important evaluation tool in Brazil, contributing to a more accurate assessment of the death and dying process and improving the quality of life and death of cancer patients at the end of life.

Several tools have been developed in an attempt to quantify/characterize QOD, including the Good-Death Scale, the Good Death Inventory (GDI), the Quality of Dying in Long-term Care (QOD-LTC), the Client Generated Index tool (CGI), the McGill Quality of Life questionnaire (MQOL) and the QoDD. The QoDD is the most widely used tool and has demonstrated greater validity and reliability than other instruments.[11]

The QODD has been widely used in QOD assessment, used and validated in different health care settings, such as in palliative care and Intensive Care Units. It is used to assess the QOD of patients reported by their family caregivers based on the six important domains of QOD symptoms: personal control, preparation for death, family concerns, treatment preferences, whole person concerns, and moment of death[4,25]

Each society has its own behaviors, beliefs, attitudes, customs and social habits that must be considered in a translation and cross-cultural adaptation process.[15,26] During this process, it is possible to identify possible translation failures, that if left unresolved, may result in difficulties in the utilization of the construct and conduction of intercultural comparative studies.[14]

As with the previous studies[24,27,28] internal consistency was also considered satisfactory ($\alpha = 0.95$). In contrast, the Cronbach's α coefficients for the domains "treatment preference" and "whole person concerns" were both below 0.7 ($\alpha = 0.686$ and $\alpha = 0.599$, respectively). However, the comparison with the previous studies is limited, as the other studies did not report the Cronbach's α values for the QoDD domains.

Two previous validations conducted correlation analyses between the QoDD and POS scores. Both studies found negative correlation coefficients ($r > 0.4$) between the total QoDD and POS scores. Although a significant correlation between the two measures was not observed, the following three QoDD domains had significant correlations with the POS total score: "symptoms and personal control;" "preparation for death;" and "whole person concerns." Unfortunately, comparisons of the POS correlations with the QoDD domains have not been previously reported, which makes comparisons difficult. In considering the QoDD a multidimensional tool, it was believed that the results should be presented not only for the total score, but also mainly for its domain scores.[24,27]

In the known-groups analysis, the QoDD was able to discriminate distinct groups of patients as hypothesized. It should be noted that the QOD scores were higher in patients cared for by palliative care specialized teams than in patients who died in wards not specialized in PC. In contrast, unlike this study's hypothesis, there was no difference in scores between dying in the hospital or at home. This may be explained by the fact that patients who died at home were not cared for by a home care team. Many Brazilian patients face socio-economic difficulties (for e.g., poverty or lack of food and medicine) that can limit their end-of-life care conditions in addition to the poor access to palliative care, which should be offered by primary care teams.

The QoDD does not make it possible to assess the death and dying wishes of the patients, so it depends on the family caregivers. This evaluation is related to the memories of family caregivers in retrospective evaluation reports, but memory, emotions, and other person-related factors may bias their reports.[29,30] To minimize these effects, the family caregivers were contacted at least 4 weeks and no later than 12 weeks after the death of the patient.

The strength of this study is the QoDD application method, which was performed through telephonic communication. This type of contact allows the caregivers to be interviewed without needing to leave their residence to participate in the interview. Since Brazil is a continental country and considering that most family members return to their cities of origin after the patient's death, a QOD questionnaire valid for usage via telephone is certainly of great clinical utility.

Taking into account that Brazil is still a country with a poor QOD,[31] it is urgent to adequately measure the QOD so that measures may be adopted at the local and public health levels. The QoDD-Br could be used as an indicator of the quality of care and to compare different health care services. It may be an useful tool to measure improvements after interventions such as staff training, after the change in protocols and availability of financial resources.

This study has a few limitations. It was restricted to only one center in Brazil in a city located in the interior of São Paulo state. However, despite the great geographic expansion of the country, all five regions share the same language, and although there are certain cultural variations, this is not a factor that hampers the generalization power of the instrument to the Brazilian population as a whole. Other psychometric properties were not evaluated, including construct validity, reliability (intra- and inter-rater reliability), and measurement error. Although a wide variety of psychometric properties may be assessed, they are not necessarily investigated in all validation studies. Thus, different validation studies may even be complementary for evaluating the same instrument.

CONCLUSION

The QoDD-Br was culturally adapted and the psychometric properties of the convergent and known-groups validities, as well as the internal consistency were analyzed. In general, the items were adequately understood by the caregivers, and the psychometric properties were considered adequate. The QoDD-Br is ready to be used as a new indicator of the quality of the dying process in Brazil. Further studies with larger sample sizes should be conducted to provide a confirmatory factor analysis, others measures of reliability, standard error of measurement, minimal detectable change, and responsiveness analysis.

REFERENCES

1. Hales S, Zimmermann C, Rodin G. The quality of dying and death. Arch Intern Med. 2008;168(9):912-8. PMID: 18474754; https://doi.org/10.1001/archinte.168.9.912.
2. Institute of Medicine (US) Committee on Care at the End of life. Approaching Death: Improving Care at the End of Life. Fiedl MK, Cassel CK, editors. Washington (DC): National Academy Press (US); 1997. PMID: 2515204.
3. Pérez-Cruz PE, Padilla Pérez O, Bonati P, et al. Validation of the Spanish version of the Quality of Dying and Death Questionnaire (QODD-ESP) in a home-based cancer palliative care program and development of the QODD-ESP-12. J Pain Symptom Manage. 2017;53(6):1042-9.e3. PMID: 28323080; https://doi.org/10.1016/j.jpainsymman.2017.02.005.
4. Patrick DL, Engelberg RA, Curtis JR. Evaluating the quality of dying and death. J Pain Symptom Manage. 2001;22(3):717-26. PMID: 11532585; https://doi.org/10.1016/s0885-3924(01)00333-5.
5. Braun M, Hasson-Ohayon I, Hales S, et al. Quality of dying and death with cancer in Israel. Support Care Cancer. 2014;22(7):1973-80. PMID: 24595406; https://doi.org/10.1007/s00520-014-2163-x.
6. Cohen LM, Germain MJ. Measuring quality of dying in end-stage renal disease. Semin Dial. 2004;17(5):376-9. PMID: 15461747; https://doi.org/10.1111/j.0894-0959.2004.17348.x.
7. Emanuel L, Bennett K, Richardson VE. The dying role. J Palliat Med. 2007;10(1):159-68. PMID: 17298264; https://doi.org/10.1089.jpm.2006.0134.
8. Knight SJ, Emanuel L. Processes of adjustment to end-of-life losses: a reintegration model. J Palliat Med. 2007;10(5):1190-8. PMID: 17985975; https://doi.org/10.1089/jpm.2006.0068.
9. Munn JC, Zimmerman S, Hanson LC, et al. Measuring the quality of dying in long-term care. J Am Geriatr Soc. 2007;55(9):1371-9. PMID: 17915342; https://doi.org/10.1111/j.1532-5415.2007.01293.x.
10. Downey L, Curtis JR, Lafferty WE, Herting JR, Engelberg RA. The Quality of Dying and Death Questionnaire (QODD): empirical domains and theoretical perspectives. J Pain Symptom Manage. 2010;39(1):9-22. PMID: 19782530; https://doi.org/10.1016/j.jpainsymman.2009.05.012.
11. Hales S, Zimmermann C, Rodin G. Review: the quality of dying and death: a systematic review of measures. Palliat Med. 2010;24(2):127-44. PMID: 20085963; https://doi.org/10.1177/0269216309351783.
12. Engelmann D, Scheffold K, Friedrich M, et al. Death-related anxiety in patients with advanced cancer: validation of the german version of the death and dying distress scale. J Pain Symptom Manage. 2016;52(4):582-7. PMID: 27521283; https://doi.org/10.1016/j.jpainsymman.2016.07.002.

13. Heckel M, Bussmann S, Stiel S, Weber M, Ostgathe C. Validation of the German version of the quality of dying and death questionnaire for informal caregivers (QODD-D-Ang). J Pain Symptom Manage. 2015;50(3):402-13. PMID: 26079825; https://doi.org/10.1016/j.jpainsymman.2015.03.020.
14. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-91. PMID: 11124735; https://doi.org/10.1097/00007632-200012150-00014.
15. Sousa VD, Rojjanasrirat W. Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-friendly guideline. J Eval Clin Pract. 2011;17(2):268-74. PMID: 20874835; https://doi.org/10.1111/j.1365-2753.2010.01434.x.
16. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42. PMID: 17161752; https://doi.org/10.1016/j.jclinepi.2006.03.012.
17. Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative care core audit project advisory group. Qual Health Care. 1999;8(4):219-27. PMID: 10847883; https://doi.org/10.1136/qshc.8.4.219.
18. Correia FR. Tradução, adaptação cultural e validação inicial no Brasil da Palliative Outcome Scale (POS). Ribeirão Preto, 2012. Available from: https://www.teses.usp.br/teses/disponiveis/22/22133/tde-27032012-153946/publico/FERNANDARIBEIROCORREIA.pdf. Accessed in 2022 (May 26).
19. Fayers PMD. Quality of Life: The Assessment, Analysis and Interpretation of Patient-Reported Outcomes. Chichester: Wiley Community; 2007.
20. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. Anesth Analg. 2018;126(5):1763-8. PMID: 29481436. https://10.1213/ANE.0000000000002864.
21. Santos IS, Tavares BF, Munhoz TN, et al. Sensibilidade e especificidade do Patient Health Questionnaire-9 (PHQ-9) entre adultos da população geral [Sensitivity and specificity of the Patient Health Questionnaire-9 (PHQ-9) among adults from the general population]. Cad Saude Publica. 2013;29(8):1533-43. PMID: 24005919; https://doi.org/10.1590/0102-311x00144612.
22. Martín M, Chan A, Dirix L, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2- advanced breast cancer (BELLE-4). Ann Oncol. 2017;28(2):313-20. PMID: 27803006; https://doi.org/10.1093/annonc/mdw562.
23. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81. PMID: 18929686; https://doi.org/10.1016/j.jbi.2008.08.010.
24. Gutiérrez Sánchez D, Cuesta-Vargas AI. Cross-cultural adaptation and psychometric testing of the quality of dying and death questionnaire for the Spanish population. Eur J Oncol Nurs. 2018;33:8-13. PMID: 29551182; https://doi.org/10.1016/j.ejon.2018.01.003.
25. Munday D, Dale J, Murray S. Choice and place of death: individual preferences, uncertainty and the availability of care. Journal of the Royal Society of Medicine. 2007;100(5):211-5. PMID: 17470927; https://10.1177/014107680710000509.
26. Cui J, Fang F, Shen F, et al. Quality of life in patients with advanced cancer at the end of life as measured by the McGill quality of life questionnaire: a survey in China. J Pain Symptom Manage. 2014;48(5):893-902. PMID: 24793079; https://doi.org/10.1016/j.jpainsymman.2014.02.016.
27. Heckel M, Bussmann S, Stiel S, Weber M, Ostgathe C. Validation of the German version of the quality of dying and death questionnaire for informal caregivers (QODD-D-Ang). J Pain Symptom Manage. 2015;50(3):402-13. PMID: 26079825; https://doi.org/10.1016/j.jpainsymman.2015.03.020.
28. Cho JY, Lee J, Lee SM, et al. Transcultural adaptation and validation of quality of dying and death questionnaire in medical intensive care units in South Korea. Acute Crit Care. 2018;33(2):95-101. PMID: 31723869; https://doi.org/10.4266/acc.2017.00612.
29. Hales S, Gagliese L, Nissim R, Zimmermann C, Rodin G. Understanding bereaved caregiver evaluations of the quality of dying and death: an application of cognitive interviewing methodology to the quality of dying and death questionnaire. J Pain Symptom Manage. 2012;43(2):195-204. PMID: 21802895; https://doi.org/10.1016/j.jpainsymman.2011.03.018.
30. Mah K, Powell RA, Malfitano C, et al. Evaluation of the quality of dying and death questionnaire in Kenya. J Glob Oncol. 2019;5:1-16. PMID: 31162985; https://doi.org/10.1200/JGO.18.00257.
31. The Economist Intelligence Unit. The 2015 quality of death index ranking palliative care across the world. 2015. Available from: https://eiuperspectives.economist.com/sites/default/files/2015%20EIU%20Quality%20of%20Death%20Index%20Oct%2029%20FINAL.pdf. Accessed in 2022 (July 15).

Authors' contributions: Paiva BSR: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Valentino TCO: formal analysis (equal), investigation (equal), methodology (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal); Mingardi M: formal analysis (equal), investigation (equal), methodology (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal); Oliveira MA: methodology (equal), formal analysis (equal), validation (equal) and writing-review and editing (equal); Franco JO: data curation (equal), investigation (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal); Salerno MC: conceptualization (equal), formal analysis (equal), investigation (equal),

methodology (equal), validation (equal) and writing-original draft (equal); Palocci H: conceptualization (equal), data curation (equal), funding acquisition (equal), investigation (equal), methodology (equal) and writing-original draft (equal); de Melo TC: data curation (equal), funding acquisition (equal), investigation (equal) and writing-original draft (equal); and Paiva CE: formal analysis (equal), investigation (equal), methodology (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal). All authors actively contributed to discussion of the study results, and reviewed and approved the final version to be released

Acknowledgments: The authors thank the Epidemiology and Biostatistics Center, Barretos Cancer Hospital, and the professionals who participated in the translation process and the expert committee. The authors extend their thanks to all the families caregivers for their time and participation in our research

Sources of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) - (grant no. 2016/11922-4) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) - (grant no. 2018/08929-2)
Conflicts of interest: The authors report no conflict of interests of any kind

Date of first submission: February 1, 2022
Last received: July 15, 2022
Accepted: August 9, 2022

Address for correspondence:
Bianca Sakamoto Ribeiro Paiva
R. Antenor Duarte Villela, 1.331
Barretos (SP) — Brasil
CEP 14784-400
Tel. (+55 17) 3321-6600 (ext. 6786)
E-mail: bsrpaiva@gmail.com

Annex 1. Original QoDD and version adapted to the Brazilian culture

Item	QoDD original version	QoDD-Br
1	*How often did X appear to have her/his pain under control?*	Com que frequência X parecia ter a dor dela/dele sob controle?...
2	*How often did X appear to have control over what was going on around her/him?*	Com que frequência X parecia ter consciência do que está acontecendo ao redor dela / dele?
3	*How often was X able to feed herself/himself?*	Com que frequência X foi capaz de alimentar-se?
4	*How often did X have control of her/his bladder or bowels?*	Com que frequência X teve controle da bexiga ou do intestino?
5	*How often did X breathe comfortably?*	Com que frequência X respirava confortavelmente?
6	*How often did X appear to feel at peace with dying?*	Com que frequência X parecia sentir-se em paz com o fato de morrer?
7	*How often did X appear to be unafraid of dying?*	Com que frequência X parecia não ter medo de morrer?
8	*How often did X laugh and smile?*	Com que frequência X ria e sorria?
9	*How often did X appear to have the energy to do most things that s/he wanted to do?*	Com que frequência X parecia ter energia para fazer a maioria das coisas que ela / ele queria fazer?
10	*How often did X appear to be worried about strain on her/his loved ones?*	Com que frequência X parecia estar preocupado (a) sobre o que seus entes queridos sentem?
11	*How often did X appear to keep her/his dignity and self-respect?*	Com que frequência X parecia manter sua dignidade e autorrespeito?
12	*How often did X spend time with her/his spouse or partner?*	Com que frequência X passava tempo com seu cônjuge ou parceira (o)?
13	*How often did X spend time with her/his children?*	Com que frequência X passava seu tempo com seu (s) filhos (as)?
14	*How often did X spend time with other family and friends?*	Com que frequência X passava seu tempo com outros familiares e amigos?
15	*How often did X spend time alone?*	Com que frequência X passava seu tempo sozinha (o)?
16	*How often did X spend time with pets?*	Com que frequência X passava seu tempo com animais de estimação
17	*Did X appear to find meaning and purpose in her/his life?*	X parecia ter encontrado sentido e propósito na vida dela/dele?
18	*Was X touched or hugged by her/his loved ones?*	X foi tocada (o) ou abraçada (o) pelos entes queridos dela/dele?
19	*Did X attend any important events - for example, weddings, graduations, and birthdays?*	X participou de algum evento importante – por exemplo, casamentos, formaturas e aniversários?
20	*Were all of X's health care costs taken care of?*	Todos os custos dos cuidados de saúde de X foram resolvidos?
21	*Did X say goodbye to the loved ones?*	X disse adeus aos seus entes queridos?
22	*Did X have one or more visits from a religious or spiritual advisor?*	X recebeu uma ou mais visitas de um conselheiro espiritual ou religioso?
23	*Did X have a spiritual service or ceremony before his/her death?*	X teve um serviço ou cerimônia espiritual antes de morrer?
24	*Was a mechanical ventilator or kidney dialysis used to prolong X's life?*	Ventilação mecânica ou hemodiálise foi usada para prolongar a vida de X?
25	*Did X have the means to end her/his life if s/he needed to?*	X tinha meios para dar um fim à vida dele (a) se ele (a) quisesse?
26	*Did X clear up any bad feelings with others?*	X esclareceu quaisquer sentimentos ruins com os outros?
27	*Did X have her/his funeral arrangements in order prior to death?*	X deixou serviço funerário dela/dele preparado antes de sua morte?
28	*Did X discuss her/his wishes for end-of-life care with her/his doctor – for example, resuscitation or intensive care?*	X discutiu seus desejos para os cuidados de fim de vida com o médico dele (a) - por exemplo, ressuscitação ou cuidado intensivo?
29	*Where did your loved one die?*	Onde seu ente querido morreu?
30	*Was anyone present at the moment of X's death?*	Alguém estava presente no momento da morte de X?
31	*In the moment before the death of X, s/he was ...*	No momento antes da morte de X, ela/ele estava ...

Association between exposure to air pollutants and hospitalization for SARS-Cov-2: an ecological time-series study

Paola Cristina Ribeiro[I], Cristóvão José Dias da Cunha[II], Adriana de Oliveira Ribeiro dos Santos[III], Bianca Rezende Lucarevschi[IV], Ana Cristina Gobbo César[V], Luiz Fernando Costa Nascimento[VI]

Department of Chemistry and Energy, Universidade Estadual de São Paulo (UNESP), Guaratinguetá (SP), Brazil

[I]MSc. Doctoral Student, Postgraduate Program on Mechanical Engineering, Department of Energy, Universidade Estadual de São Paulo (UNESP), Guaratinguetá (SP), Brazil.
https://orcid.org/0000-0002-1252-5731

[II]MSc. Doctoral Student, Postgraduate Program on Mechanical Engineering, Department of Energy, Universidade Estadual de São Paulo (UNESP), Guaratinguetá (SP), Brazil.
https://orcid.org/0000-0002-1252-2368

[III]MD, PhD. Assistant Professor, Department of Medicine, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil.
https://orcid.org/0000-0002-5940-9522

[IV]MD, PhD. Assistant Professor, Department of Medicine, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil.
https://orcid.org/0000-0001-9723-4126

[V]PhD. Assistant Professor, Instituto Federal de Educação Ciência e Tecnologia de São Paulo (IFSP), Campus Bragança Paulista (SP), Brazil.
https://orcid.org/0000-0001-8618-8654

[VI]MD, PhD. Researcher, Postgraduate Program on Mechanical Engineering, Universidade Estadual de São Paulo (UNESP), Guaratinguetá (SP), Brazil; and Researcher, Postgraduate Program on Environmental Sciences, Universidade de Taubaté (UNITAU), Taubaté (SP), Brazil.
https://orcid.org/0000-0001-9793-750X

KEY WORDS (MeSH terms):
SARS-Cov-2.
Air pollutants.
Nitrogen dioxide.

AUTHORS' KEY WORDS:
Fine particulate matter.
Costs.
2019 novel coronavirus.

ABSTRACT

BACKGROUND: Exposure to air pollutants and illness by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection can cause serious pulmonary impairment.

OBJECTIVE: To identify a possible association between exposure to air pollutants and hospitalizations due to SARS-Cov-2.

DESIGN AND SETTING: Ecological time-series study carried out in Taubaté, Tremembé, and Pindamonhangaba in 2020 and 2021.

METHODS: Study with Sars-Cov-2 hospitalizations with information on hospitalization date, sex and age of the subjects, duration of hospitalization, type of discharge, and costs of these hospitalizations. Statistical analysis was performed through a negative binomial regression, with data on pollutant concentrations, temperature, air relative humidity, and hospitalization date. Coefficients obtained by the analysis were transformed into relative risk for hospitalization, which estimated hospitalizations excess according to an increase in pollutant concentrations.

RESULTS: There were 1,300 hospitalizations and 368 deaths, with a predominance of men (61.7%). These data represent an incidence rate of 250.4 per 100,000 inhabitants and 28.4% hospital lethality. Significant exposure (P value < 0.05) occurred seven days before hospital admission (lag 7) for nitrogen dioxide (NO_2) (relative risk, RR = 1.0124) and two days before hospital admission for $PM_{2.5}$ (RR = 1.0216). A 10 μg/m^3 in NO_2 concentration would decrease by 320 hospitalizations and » US $ 240,000 in costs; a 5 μg/m^3 in $PM_{2.5}$ concentration would decrease by 278 hospitalizations and » US $ 190,000 in costs.

CONCLUSION: An association between exposure to air pollutants and hospital admission due to Sars-Cov-2 was observed with excess hospitalization and costs for the Brazilian public health system.

INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic first detected in Wuhan, China, in December 2019.[1] COVID-19 is a highly transmissible and fatal syndrome-induced disease, followed by severe acute respiratory disease. Typically, COVID-19 infected patients show mild to moderate symptoms, including sore throat, fever, shortness of breath, dry cough, and loss of smell and taste, while it causes pneumonia with severe acute respiratory syndrome (SARS), kidney failure, and even death in some patients.[2,3]

Initially described in December 2019 in Wuhan City, capital of China's Hubei Province, it became the center of an outbreak of pneumonia of unknown cause. In January 2020, scientists isolated a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as 2019-nCoV.[4]

Exposure to air pollutants has been linked to hospitalizations, respiratory diseases, cardiovascular diseases, and death.[5-8] However, studies have been carried out associating air pollution, and hospitalizations, and deaths from COVID-19; other studies have shown the interrelationship of short-term and chronic exposure to ambient air pollution and COVID-19 infection.[9,10] Among these pollutants is nitrogen dioxide (NO_2), a nitrogen-centered free radical mainly produced in urban areas by traffic. Ozone (O_3) is a secondary atmospheric pollutant composed of three oxygen atoms formed at ground level by NO_2 reactions and volatile organic compounds with sunlight.

Particulate matter is a mixture of liquid, solid, or solid and liquid particles suspended in the air and is composed of a carbonaceous core of organic compounds (polycyclic aromatic hydrocarbons, PAHs), inorganic compounds (transition metals, sulfates, and nitrates), and biological

components (bacteria, fungi, and viruses). Particulate matter is categorized according to size, PM_{10}, and its fine fraction $PM_{2.5}$ with aerodynamic diameters of less than 10 and 2.5 microns, respectively.[11]

OBJECTIVE

This study aimed to identify possible associations between exposure to air pollutants and hospitalizations due to COVID-19 in residents of the conurbation cities of Taubaté, Tremembé, and Pindamonhangaba, SP, given the fact that exposure to air pollutants is associated with diseases of the respiratory system and COVID-19 is a respiratory system's disease.

METHODS

An ecological time-series study was carried out with data on hospitalization due to COVID-19 in residents of the conurbation cities of Taubaté, Tremembé, and Pindamonhangaba, located in Paraíba valley of São Paulo State, between April 1, 2020, and March 31, 2021.

The city of Taubaté is located between two large metropolises, Rio de Janeiro and São Paulo. With a humid subtropical climate at 580 meters above sea level, it is located in the region of the Paraíba valley and has great economic importance, predominantly industrial. With approximately 320,000 inhabitants and an area of 625 km^2, it is considered a medium-sized city. However in the winter months, it can present peaks of pollution of fine particulate matter. This can also be attributed to the fact that the city is cut by one of the most important highways in the country, the Dutra Highway, in addition to being surrounded by the Serra do Mar and Serra da Mantiqueira, making it difficult to disperse pollutants.[12]

The city of Tremembé has about 50,000 inhabitants and an area of approximately 190 km^2; considered a tourism resort, it has an urban area combined with the city of Taubaté; the city also has territory limits with other cities such as Pindamonhangaba, Monteiro Lobato, and Santo Antonio do Pinhal. The city of Pindamonhangaba has about 150,000 inhabitants and an approximate area of 730 km^2. Tremembé, is also linked with Taubaté. Its economy is mainly in the service sector, followed by industry, with a humid subtropical climate at an altitude of 540 meters above sea level. Both cities are part of the metropolitan region of Vale do Paraíba.[12]

Department of Information Technology of the Unified Health System (DATASUS) provided daily values of hospitalizations,[13] and according to the Hospital Information System of the SUS (SIHSUS) with diagnosis B34.2, which is in accordance with the ICD-10 depending on age, days of stay, date of admission, sex and type of discharge - discharge or death, and costs of admissions for both discharge and death. This SIHSUS information system has the accounting conference of hospitalizations as its main purpose. Still, it provides data such as those mentioned above that are used for studies on exposure to air pollutants and hospitalizations.

The Environmental Company of the State of São Paulo (CETESB)[14] provided the daily values of pollutant concentrations: particulate matter with an aerodynamic diameter smaller than 2.5 u ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3), in addition to data of daily temperature and relative humidity, and a correlation matrix was built with these variables.

Poisson's probability distribution is the closest to the frequency of hospitalizations since it involves discrete and counting data, with an excess of zeros and asymmetric and asymptotic distribution; however, these data may have a different mean from the variance and, for this reason, the multivariate model of negative binomial regression was used.

A multipollutant model with a confidence interval of 95% was used for the analyses, in addition to a lag period of 0 to 7 days (lag 0-7) because the effect of pollutants can be felt days after exposure. Such coefficients (coeff) were transformed into relative risk (RR), as shown in the equation: RR = exp (coeff).

In the analyses, a percentual increment (PI) of 10 $\mu g/m^3$ in concentrations of pollutant NO_2 and 5 $\mu g/m^3$ in concentrations of $PM_{2.5}$ were calculated for both sexes, represented in relative risk [RR], demonstrated in the equation PI = ([exp (ß*ΔC) -1] *100) where: ß is the value obtained from negative binomial regression, and ΔC is the variation of the pollutant concentration.

Proportional attributed risk (PAR) was used, where PAR = [1 – (1/RR)], according to PI effects in the concentration of NO_2 and $PM_{2.5}$, to estimate, in percentages, the impact of these increases in hospitalizations due to COVID-19. The excess of hospitalizations was calculated using the equation PAF = (PAR * N), where PAR is described above, and N is the number of hospital admissions for both sexes. The number of hospital admissions that led to death and the total cost was obtained from the DATASUS site.

The chance of death (OR) according to sex was calculated with a confidence interval of 95%. Student's t-test was used; to compare the mean age and length of stay according to sex and type of discharge – death or alive; alpha = 0.05 was the significance level adopted in this study.

The present study was not submitted to the Research Ethics Committee, as we did not have access to identifying patients during hospitalizations.

RESULTS

A total of 1,300 cases hospitalized by CID B34.2 were identified in the three cities from April 1, 2020, to March 31, 2021. Of these hospitalizations, 742 (57.1%) correspond to males and 558 (42.9%) to females. Regarding the cases that led to death, the total was 370 (28.4%), with 229 (61.9%) corresponding to males and 141 (38.1%) to females; regarding the days of stay, according to sex, there was no statistical difference, with males having an average of 9.5 days (± 9.3) and females an average of 9.6 days (± 10.7) (P value = 0.80). The average age of admissions of adults >50 years was evident, and

the average age of admissions for males was 60.2 years (± 16.6), and the average age for the female gender was 59.1 years (± 16.8), (P value = 0.23), and it can be seen in **Table 1**.

These data represent an incidence rate of 250.4 cases per 100,000 inhabitants and hospital lethality of 28.4%.

The length of stay of patients hospitalized for SARS-CoV-2 who died had an average of 12.3 (± 10.9) days, while in hospitalizations that were discharged, it was 8.5 days (± 9.3) (P value < 0.01). Analyzing hospitalizations that resulted in death, the mean age was 67.6 years (± 13.6), while the mean age of patients who were discharged was 56.8 years (± 16.6) (P value < 0.01), demonstrating that older patients are more likely to die when hospitalized.

A significant association of deaths was noted in males OR = 1.30 (95% confidence interval, CI 1.06-1.65).

The concentration of pollutants observed in the period presented an average within the standards established by the WHO, but when observing the days separately, it can be noted that the pollutant $PM_{2.5}$ presented a maximum peak of 63 µg/m³, and the maximum daily value considered safe by the WHO is 25 µg/m³. Ozone also recorded values above WHO standards, with a peak of 110 µg/m³. NO_2 remained within the acceptable standard during the study period. The pollutant values can be seen in **Table 2**. The values provided by Pearson's correlation matrix for the study variables are in **Table 3**.

The daily values of cases, as well as the values of significant concentrations of air pollutants found in the study period, are shown in **Figures 1-A**, **1-B**, and **1-C**.

Table 1. Hospitalizations, numbers of discharges and deaths by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), length of stay, and age, separated by sex in the conurbated cities of Taubaté, Tremembé and Pindamonhangaba, from March 2020 to April 2021

Variable	Male	Female	Total
Cases	742 (57.1%)	558 (42.9%)	**1,300 (100%)**
Deaths	229 (61.9%)	141 (38.1%)	**370 (100%)**
Length of stay (days)	9.5 (± 9.3)#	9.6 (± 10.7)#	
Age (years)	60.2 (± 16.6)#	59.1 (± 16.8)#	

#Standard deviation.

Table 2. Values of mean, standard deviation (SD), maximum (max) and minimum (Min) of pollutants concentrations* (ug/m³), and meteorological variables** in the conurbated cities of Taubaté, Tremembé and Pindamonhangaba, from March 2020 to April 2021

Variable	Mean	SD	Min	Max
NO_2	30.5	16.96	4	110
O_3	69.2	21.07	28	131
$PM_{2.5}$	13.9	7.35	4	63
RH (%)	43.2	14.19	16	90
MT (ºC)	22.1	3.15	12.8	30.5

*NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = fine particulate matter; **RH = relative humidity; MT = mean temperature.

Table 3. Pearson's correlation matrix between all atmospheric variables, in the conurbated cities of Taubaté, Tremembé and Pindamonhangaba, from March 2020 to April 2021

	NO_2 (ug/m³)	O_3 (ug/m³)	$PM_{2.5}$ (ug/m³)	RH (%)	Temp ºC
NO_2 (ug/m³)	1				
O_3 (ug/m³)	0.17**	1			
$PM_{2.5}$ (ug/m³)	0.51 **	0.51 **	1		
RH (%)	-0.38 **	0.60**	-029**	1	
Temp ºC	-0.11**	0.55**	0.06	0.34**	1

$PM_{2.5}$ = fine particulate matter; NO_2 = nitrogen dioxide; O_3 = Ozone; RH = relative humidity.

*P value < 0.05; **P value < 0.01

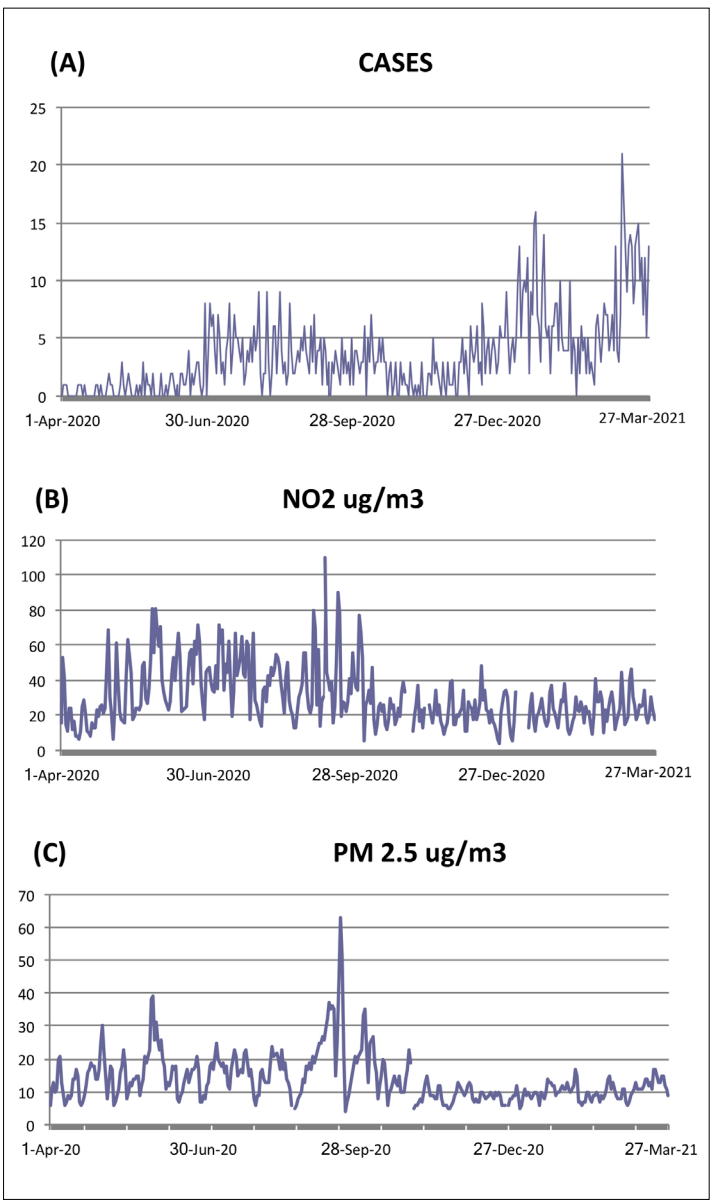


Figure 1. Daily values, shown in quarters, of cases (**A**), of mean concentrations of NO_2 in ug/m³ (**B**) and of mean concentrations of $PM_{2.5}$ in ug/m³ (**C**) in the conurbated cities of Taubaté, Tremembé and Pindamonhangaba, from April 2020 to March 2021.

When the hospitalizations that led to death were correlated with atmospheric pollutants in the multi-pollutant model, exposure to O_3 did not show statistical significance, but exposure to NO_2 and $PM_{2.5}$ pollutants showed positive significance in relation to hospitalizations.

NO_2 presented significance to the pollutant at different times with the following relative risk values and their respective confidence intervals: lag 0 [RR = 1.0108 95% CI (1.0034-1.0183)], lag 1 [RR = 1.0072 95% CI (1.0003-1.0143)], lag 3 [RR = 1.0088 95% CI (1.0018-1.0159)] and lag 7 [RR = 1.0124 95% CI (1.0051-1.0197)], whereas the pollutants $PM_{2.5}$ showed a positive association, later when compared to NO_2. Nevertheless, with the fine particulate matter ($PM_{2.5}$) an association can be observed at three different times with the following relative risk values and their respective confidence intervals: lag 2 [RR = 1.0216 95% CI (1.0032-1.0403)], lag 5[RR = 1.0199 95% CI (1.0016-1.0387)] and lag 6 [RR = 1.0186 95% CI (1.0002-1.0373)].

Both hospitalizations that were discharged and hospitalizations that led to death generated costs of approximately R$ 8 million (≈ US$ 1.6 million); hospitalizations that required intensive care were responsible for 65% of the costs, and hospitalizations that resulted in death were responsible for R$ 4.5 million (≈ 51% of the total). The costs presented correspond to the hospitalizations from April 2020 to March 2021.

Relative risk index values can be seen in **Figure 2-A** (NO_2) and **Figure 2-B** ($PM_{2.5}$) according to an increment of 10 μg/m³ in concentrations of $PM_{2.5}$ and NO_2.

With an increase of 10 μg/m³ of NO_2 and $PM_{2.5}$ concentrations, there would be a percentage increase of 24% and 21% in hospitalizations, corresponding to 320 and 278 hospitalizations, respectively. Thus, with the reduction in the concentrations of these pollutants, as explained above, for NO_2, there would be savings of around R$1.2 million (≈ US$ 240 thousand) in the cost of hospitalizations. For $PM_{2.5}$, the reduction would reach approximately R$ 970 thousand (≈ US$ 190 thousand) in cases of hospitalization.

DISCUSSION

This study identified hospitalization and lethality rates for SARS-Cov-2 in the conurbation cities of Taubaté, Tremembé, and Pindamonhangaba, showing a positive association with exposure to NO_2 and $PM_{2.5}$, while exposure to O_3 showed a non-significant association; such data provide a basis for further studies to be carried out in other regions, especially the heavily polluted ones.

Effects were noted at lags 0, 1, 3, and 7 for exposure to NO_2 and lag 2, 5, and 6 for $PM_{2.5}$.

The data obtained represent an incidence rate of 250.4 cases per 100,000 inhabitants and a case fatality rate of 28.4%, with both hospitalizations and deaths predominating in males.

A study carried out with data of the SIVEP-Gripe official system of the Ministry of Health, obtained between February 2020 and May 2021, identified 366,802 cases and 106,437 deaths for the entire state of São Paulo. This indicates an accumulated incidence of 858.6 cases per 100,000 inhabitants and a mortality rate of 259.1 per 100,000 inhabitants; these values, well above those found in our study, may be associated with geographic differences and differences in the source of data collection. Males had a higher prevalence of hospitalizations and deaths than females, which was similar to the findings of our study.[15] The same behavior was found by Peres et al.[16] and Klokner et al.[17]

This relatively unequal incidence and mortality in men can be interpreted considering many factors: the comparatively higher prevalence of comorbidities (hypertension, diabetes, cardiovascular

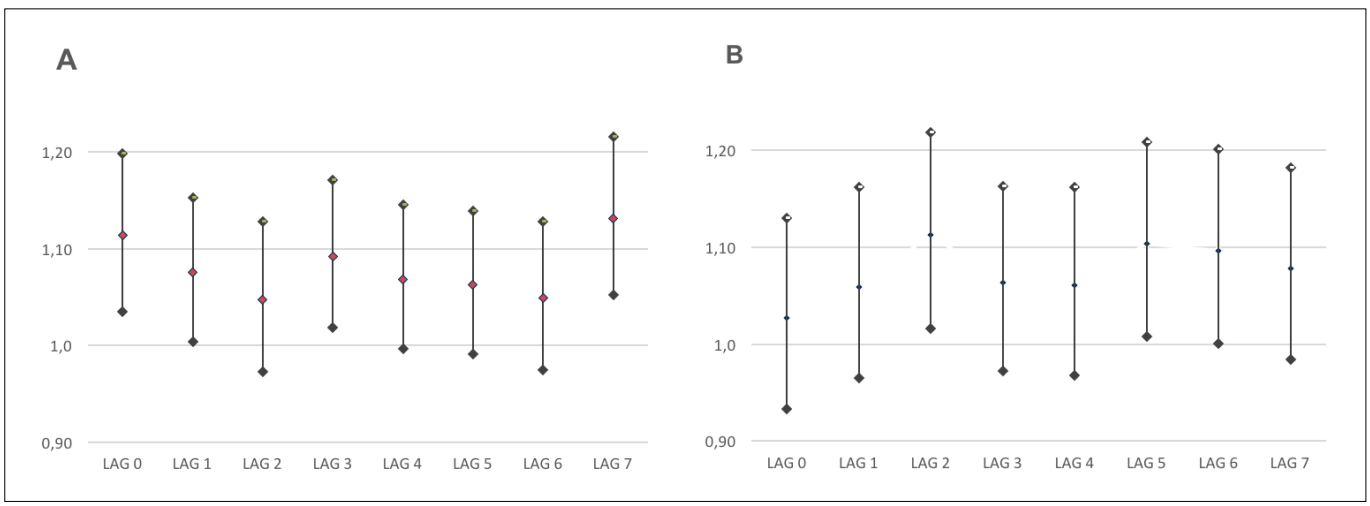


Figure 2. Relative risks for hospitalization due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), according to a 10 ug/m³ increase in NO_2 (**A**) and $PM_{2.5}$ (**B**) concentrations according to lags from 0 to 7 days in the conurbated cities of Taubaté, Tremembé and Pindamonhangaba, from April 2020 to March 2021.

diseases, and chronic lung diseases), more risk behaviors (smoking and alcohol use), and exposure to occupational and sex differences in immune responses.[18,19]

In a study carried out in India, where the concentrations of $PM_{2.5}$ were 88.3 ug/m^3 and those of NO_2, 36.5 ug/m^3, associations were also identified between exposure to these pollutants and new cases of COVID-19 as well as an association with new deaths.[20]

Daily confirmed cases in 120 Chinese cities were obtained from January 23, 2020, to February 29, 2020, where significantly positive associations were observed for $PM_{2.5}$ and NO_2 exposure. A 10 μg/m^3 (lag 0-14) increase in $PM_{2.5}$ and NO_2 was associated with 2.24% (95% CI: 1.02 to 3.46) and 6.94% (95% CI: 2.38 to 11.51) in the daily count of confirmed cases, respectively.[21]

In two regions of northern Italy, with tropospheric nitrogen data estimated by satellite, even with low model accuracy, it was possible to identify an association between high concentrations of NO_2 and deaths from COVID-19, which provides evidence supporting a pollution effect in increasing the proportion of fatal cases of the disease. The association was stronger when using the longer-term cumulative mortality as an outcome.[22]

Another important data revealed in this study is the cost of these hospitalizations. Hospitalizations that resulted in hospital discharge cost R$ 3,526,328.67, and the hospital cost for patients who died cost R$ 4,538,663.57; hospitalizations that resulted in death and that required intensive care (ICU) cost twice as much as those that resulted in ICU discharge.

If they reduced 5 μg/m^3 of the pollutant $PM_{2.5}$ in the atmosphere and 10 μg/m^3 of the pollutant NO_2, in the case of the studied region, the savings could be up to R$ 1.2 million.

The mechanisms involved are still poorly understood. It is believed that increased oxidative stress is the key mechanism of pollutant-induced toxicity and that $PM_{2.5}$ suspended in the atmosphere would facilitate viral survival and promote its atmospheric transport. Exposure to air pollutants promotes viral entry, replication, and assembly, which cause increased local inflammation due to reduced mucociliary clearance, modulation of cellular pathways, and increased epithelial permeability because of decreased junction proteins with a substantial increase in viral spread and inflammation due to permeable epithelium, prevention of macrophage uptake and defects in natural killer (NK) cell functions with amplification of inflammation and neutrophil recruitment plus increased virus-induced tissue damage and inflammation. This sequence of events leads to fluid accumulation in the alveoli, respiratory failure, and death.[23]

This study had limitations. First, due to ecological studies, the type of information obtained from an official source might have a diagnostic error. Second, the address of the subject who informed it possibly wrongly. Third, lack of information on co-morbidities might have contributed to the impossibility of assessing the importance of risk factors mentioned in the literature and estimating their importance in the number of cases. Moreover, exposure to pollutants might not be indicated as a cause of infection by COVID-19, but an association between exposure and cases.

CONCLUSION

Regardless of what might have caused the possible abovementioned limitations, it was possible to identify an association between exposure to $PM_{2.5}$ and NO_2 pollutants in hospitalizations due to COVID-19, in addition to the total cost of these hospitalizations.

REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol. 2020;92(4):401-2. PMID: 31950516; https://doi.org/10.1002/jmv.25678.
2. Dong, E, Hongru D, Lauren G. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4. Erratum in: Lancet Infect Dis. 2020;20(9):e215. PMID: 32087114; https://doi.org/10.1016/S1473-3099(20)30120-1.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. PMID: 32171076. https://doi.org/10.1016/S0140-6736(20)30566-3.
4. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. JAMA. 2020;323(8):709-10. PMID: 31999307; https://doi.org/10.1001/jama.2020.1097.
5. César ACG, Nascimento LF. Coarse particles and hospital admissions due to respiratory diseases in children. An ecological time series study. Sao Paulo Med J. 2018;136(3):245-50. PMID: 29947697; https://doi.org/10.1590/1516-3180.2017.0362080218.
6. Machin AB, Nascimento LFC. Effects of exposure to air pollutants on children's health in Cuiabá, Mato Grosso State, Brazil. Cad Saude Publica. 2018;34(3):e00006617. PMID: 29538512; https://doi.org/10.1590/0102-311X00006617.
7. Machin AB, Nascimento LF, Mantovani K, Machin EB. Effects of exposure to fine particulate matter in elderly hospitalizations due to respiratory diseases in the South of the Brazilian Amazon. Braz J Med Biol Res. 2019;52(2):e8130. PMID: 30698228; https://doi.org/10.1590/1414-431X20188130.
8. Xie J, Teng J, Fan Y, Xie R, Shen A. The short-term effects of air pollutants on hospitalizations for respiratory disease in Hefei, China. Int J Biometeorol. 2019;63(3):315-26. PMID: 30680626; https://doi.org/10.1007/s00484-018-01665-y.
9. Fattorini D, Regoli F. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. Environ Pollut. 2020;264:114732. PMID: 32387671; https://doi.org/10.1016/j.envpol.2020.114732.
10. Frontera A, Cianfanelli L, Vlachos K, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: The "double-

hit" hypothesis. J Infect. 2020;81(2):255-9. PMID: 32447007; https://doi.org/10.1016/j.jinf.2020.05.031.

11. WHO (World Health Organization). WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide: Global update 2005: Summary of risk assessment. Geneva: WHO; 2006. Available from: https://wedocs.unep.org/bitstream/handle/20.500.11822/7493/-WHO_air_quality_guidelines_for_particulate_matter%2c_ozone%2c_nitrogen_dioxide_and_sulfur_dioxide_Global_update_2005_Summary_of_risk_assessment-2006WHO.pdf?sequence=3&isAllowed=y. Accessed in 2022 (Apr 6).
12. Brasil. Instituto Brasileiro de Geografia e Estatística - IBGE. População no último censo. Available from: http://cidades.ibge.gov.br/xtras/perfil.php?codmun=355410. Accessed in 2022 (Apr 6).
13. Brasil. Ministério da Saúde. Departamento de Informática do SUS - DATASUS. Available from: https://datasus.saude.gov.br/. Accessed in 2022 (Apr 6).
14. São Paulo. Companhia Ambiental do Estado de São Paulo – CETESB. Available from: https://cetesb.sp.gov.br/. Accessed in 2022 (Apr 6).
15. Lorenz C, Ferreira PM, Masuda ET, et al. COVID-19 in the state of São Paulo: the evolution of a pandemic. Rev Bras Epidemiol. 2021;24:e210040. PMID: 34495193; https://doi.org/10.1590/1980-549720210040.
16. Peres IT, Bastos LSL, Gelli JGM, et al. Sociodemographic factors associated with COVID-19 in-hospital mortality in Brazil. Public Health. 2021;192:15-20. PMID: 33607516; https://doi.org/10.1016/j.puhe.2021.01.005.
17. Klokner SGM, Luz RA , Araujo PHM , et al. Perfil epidemiológico e preditores de fatores de risco para a COVID-19 na região sul do Brasil. Research, Society and Development. 2021;10(3):e17710313197. https://doi.org/10.33448/rsd-v10i3.13197.
18. Sharma G, Volgman AS, Michos ED. Sex Differences in Mortality From COVID-19 Pandemic: Are Men Vulnerable and Women Protected? JACC Case Rep. 2020;2(9):1407-10. PMID: 32373791; https://doi.org/10.1016/j.jaccas.2020.04.027.
19. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626-38. PMID: 27546235; https://doi.org/10.1038/nri.2016.90.
20. Singh A. Ambient air pollution and COVID-19 in Delhi, India: a time-series evidence. Int J Environ Health Res. 2021:1-14. PMID: 34538153; https://doi.org/10.1080/09603123.2021.1977258.
21. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. Sci Total Environ. 2020;727:138704. PMID: 32315904; https://doi.org/10.1016/j.scitotenv.2020.138704.
22. Filippini T, Rothman KJ, Cocchio S, et al. Associations between mortality from COVID-19 in two Italian regions and outdoor air pollution as assessed through tropospheric nitrogen dioxide. Sci Total Environ. 2021;760:143355. PMID: 33187703; https://doi.org/10.1016/j.scitotenv.2020.143355.
23. Woodby B, Arnold MM, Valacchi G. SARS-CoV-2 infection, COVID-19 pathogenesis, and exposure to air pollution: What is the connection? Ann N Y Acad Sci. 2021;1486(1):15-38. PMID: 33022781; https://doi.org/10.1111/nyas.14512.

Authors' contributions: Ribeiro PC: conceptualization, methodology, validation, and writing-review; Cunha CJD: conceptualization, formal analysis, software, and writing-review; Santos AOR: formal analysis, project administration, supervision, writing-review; Lucarevschi BR: review and editing, data curation, conceptualization, and writing-review; César ACG: review and editing; data curation; conceptualization methodology; and Nascimento LFC: conceptualization, formal analysis, methodology, and writing-review and editing. All authors actively contributed to the discussion of the study results and reviewed and approved the final version to be released

Sources of funding: None
Conflicts of interest: None

Date of first submission: April 3, 2022
Last received: July 13, 2022
Accepted: August 9, 2022

Address for correspondence:
Luiz Fernando Costa Nascimento
Av. Ariberto Pereira da Cunha, 333
Guaratinguetá (SP) — Brasil
CEP 12516-410
Tel. (+55 12) 3123-2161
E-mail: fernando.nascimento@unesp.br

Determinants of poor sleep quality in adults during the coronavirus disease pandemic: *COVID-Inconfidentes*, a population-based study

Luiz Antônio Alves de Menezes Júnior[I], Luciano Garcia Lourenção[II], Amanda Cristina de Souza Andrade[III], Júlia Cristina Cardoso Carraro[IV], George Luiz Lins Machado-Coelho[V], Adriana Lúcia Meireles[VI]

Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil, and Universidade Federal do Rio Grande (FURG), Rio Grande (RS), Brazil

[I]MSc. Nutritionist and Doctoral Student, Postgraduate Program in Health and Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-4497-5358

[II]MSc, PhD. Nurse and Associated Professor, Nursing School, Universidade Federal do Rio Grande (FURG), Rio Grande (RS), Brazil.
https://orcid.org/0000-0002-1240-4702

[III]MSc, PhD. Statistics and Associated Professor, Institute of Collective Health, Universidade Federal do Mato Grosso (UFMT), Cuiabá (MT), Brazil.
https://orcid.org/0000-0002-3366-4423

[IV]PhD. Nutritionist and Associated Professor, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0003-0027-2690

[V]MD, MSc, PhD. Epidemiologist and Associated Professor, School of Medicine, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-9806-9721

[VI]MSc, PhD. Nutritionist and Associated Professor, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-1447-953X

KEY WORDS (MeSH terms):
Coronavirus infections.
Sleep deprivation.
Health surveys.
Body weight changes.
Sunlight.
Anxiety.

AUTHORS' KEY WORDS:
Coronavirus disease.
Insufficient sleep.
Anxiousness.
Sleep latencies.
Vitamin D deficiencies.
Hygiene, Sleep.

ABSTRACT

BACKGROUND: The coronavirus disease (COVID-19) pandemic has adversely affected the health of the global population, with sleep quality being one of the affected parameters.

OBJECTIVES: To evaluate sleep quality and its associated factors in adults during the COVID-19 pandemic in Brazil.

DESIGN AND SETTING: A population-based cross-sectional serological survey of 1,762 adults in the Iron Quadrangle region of Brazil.

METHODS: The Pittsburgh Sleep Quality Index was used to assess sleep quality. Sociodemographic variables, health conditions, health-related behaviors, anxiety, vitamin D levels, weight gain/loss, and pandemic characteristics were assessed using a structured questionnaire. Univariate and multivariate analyses using Poisson regression with robust variance were performed to identify factors associated with sleep quality.

RESULTS: More than half of the participants reported poor sleep quality (52.5%). Multivariate analysis revealed that the factors associated with poor sleep quality included living alone (prevalence ratio [PR] = 1.34; 95% confidence interval [CI]: 1.04–1.73), anxiety disorder (PR = 1.32; 95% CI: 1.08–1.62), 5.0% weight loss (PR = 1.21; 95% CI: 1.02–1.44), 5.0% weight gain (PR = 1.27; 95% CI: 1.03–1.55), vitamin D deficiency (PR = 1.16; 95% CI: 1.01–1.35), and COVID-19 symptoms (PR = 1.29; 95% CI: 1.10–1.52).

CONCLUSIONS: Our study revealed that more than half of the participants experienced poor sleep quality during the COVID-19 pandemic. Factors associated with poor sleep quality included vitamin D deficiency and weight changes related to the pandemic.

INTRODUCTION

Sleep is essential for maintaining physiological parameters and plays an important role in hormone release and the regulation of cardiovascular activities and glucose levels.[1] In addition, Poor sleep quality, particularly if chronic, may adversely affect the immune system components, disrupting antibody production after vaccination or previous contact with the viral agent. This could lead to increased vulnerability to infectious diseases such as coronavirus disease (COVID-19).[2]

From the beginning of the pandemic to almost two years later, Brazil has been one of the most affected countries. It remains in the top five countries with highest number of infected people and deaths due to COVID-19.[3] Owing to the highly contagious nature of COVID-19 and limited knowledge regarding its natural history, several control measures have been adopted, such as practice of respiratory hygiene, use of masks, and implementation of social restrictions.[4]

These measures, along with the pandemic scenario, have led to drastic changes in people's lifestyle, such as reduced physical activity, changes in food intake, reduced sun exposure,[4,5] and other factors that directly affect sleep quality.[6,7]

OBJECTIVE

As a pandemic tends to alter the daily routine and life habits of the population,[8] this study aimed to evaluate sleep quality and its associated factors during the COVID-19 pandemic.

METHODS

Study design

This cross-sectional household population-based serological study is part of the COVID-*Inconfidentes* project (Epidemiological Surveillance of COVID-19 in the region of *Inconfidentes*, Minas Gerais). In this study, a seroepidemiological survey of 1,762 adults was conducted to determine the prevalence of COVID-19 and perform a situational assessment of the health-related aspects of this population. Data were collected on weekends between October and December 2020 in two medium-sized cities located in the central region of the state of Minas Gerais, known as the Iron Quadrangle. The Research Ethics Committee of the Federal University of Minas Gerais approved this project on September 22, 2020 (certificate of ethics submission: No. 32815620.0.1001.5149). All procedures adopted in this study were in accordance with the principles of the Declaration of Helsinki and the Brazilian guidelines and standards for human research. Written informed consent was obtained from all participants.

The survey was conducted in three stages at 21-day intervals, and different census sectors were evaluated in each city. The complex sample size calculation was based on the population estimate for each city, considering a confidence level of 95%, design effect of 1.5, and the parameters presented in a previous study.[9]

A three-stage conglomerate sampling design was adopted as follows: census sector (randomly selected for each stage and without replacement), households (selected by a systematic sampling process), and residents (one resident selected randomly). The sample weight of each selected unit (census tract, household, and individual) was calculated and adjusted to compensate for the loss of interviews owing to non-response, and the weights of the household and the selected resident were calibrated.[9]

Data collection

The data collection process included listing and approaching households during weekends to enhance the participation of residents who worked during the week, thus increasing the representativeness of this population group.

Face-to-face interviews were conducted by trained interviewers, using a structured questionnaire to collect data on sociodemographic variables, health conditions, pandemic characteristics, and sleep quality. Sociodemographic variables included sex, age, marital and living status, education, family income, employment status (yes or no), and current work shift. Furthermore, we evaluated the work-from-home schedule. Health conditions included self-reported chronic diseases, divided into those with morbidity (reporting at least one disease) and without morbidity (no disease). Individuals were also assessed for chronic physical pain (physical pain present for ≥ 3 months), current smoking habit and alcohol consumption, and physical activity (grouped into: inactivity, at least 150–300 minutes of moderate-intensity aerobic physical activity per week, or at least 75–150 minutes of vigorous-intensity aerobic physical activity per week).[10] Self-rated health was assessed as "very good," "good," "fair," "poor," and "very poor".

Nutritional status was assessed based on body mass index (BMI). Self-reported weight and height were used to calculate BMI. Based on the BMI, the participants were classified as underweight (BMI < 18.5 kg/m² if aged < 60 years; BMI < 23.0 kg/m² if aged ≥ 60 years), eutrophic (BMI 18.5–24.9 kg/m² if aged < 60 years; BMI 23.0–28.0 kg/m² if aged ≥ 60 years), and overweight (BMI ≥ 25.0 kg/m² if aged < 60 years; BMI ≥ 28.0 kg/m² if aged ≥ 60 years).[11,12] We also evaluated their weight change during the pandemic, according to the weight measured before and during the pandemic. To account for variability in weight change owing to differences in body mass, the percent change in total body weight from before the pandemic (March 2020) to the time of data collection (October to December 2020) was determined. A change in weight of ≥ 5% of body weight (gain or loss) was defined as a clinically significant change. Several studies have reported that a 5% gain in body weight has significant clinical effects not only on the risk of cardiovascular disease and diabetes mellitus[13,14] but also on chronic pain,[15] which is an important determinant of sleep quality.[16] In addition, it has been recommended as a threshold for clinically relevant weight loss in several national and international guidelines.[17-20]

The average daily sun exposure was evaluated and classified as "insufficient" if exposure was < 30 minutes/day and "sufficient" if it was ≥ 30 minutes/day.[21] We also evaluated a possible scenario of vitamin D deficiency, considering the extent of the time of sun exposure and consumption of food supplements fortified with vitamin D. Since there is no specific recommendation to determine sufficient vitamin D levels, we used the recommendations of Holick (2007) to classify the proposed components, which included an average sun exposure of 30 minutes or consumption of a supplement source of vitamin D (vitamin D sufficiency).[21]

Responses related to the COVID-19 pandemic were evaluated, such as presenting with at least one symptom in the last 15 days, social restriction since the beginning of the pandemic, any family member in the COVID-19 risk group, and the pandemic period. Furthermore, we asked about their daily routine activities during the pandemic.

Measurement of sleep quality

The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to assess sleep quality. This instrument comprises 19 questions categorized into seven components: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleep medication

(C6), and daytime dysfunction (C7). The sum of the scores produces an overall score in the range of 0–21, with the highest score indicating the worst sleep quality. An overall score of > 5 indicates major difficulties in at least two components or moderate difficulties in more than three components.[22] The Brazilian version of the PSQI has an overall reliability coefficient (Cronbach α) of 0.82, indicating a high degree of internal consistency.[23]

Herein, sleep quality was classified as good (PSQI score ≤ 5) or poor (PSQI score > 5). A PSQI score of ≥ 2 indicated moderate to severe difficulty in a sleep-specific domain (C1 to C7).[22] This cut-off point was also used by Wang et al. in their study in 2020.[24]

Statistical analysis

Statistical analyses were performed considering the complex design of the sample using the "svy" command of the Stata software (version 15.0; Stata Corp, College Station, Texas, United States). Data are presented as percentages and 95% confidence intervals (CI). Data were compared using the chi-square test and Bonferroni correction for multiple tests.[25] Univariate and multivariate analyses were used to determine the association between sleep quality and sociodemographic factors, health conditions, and COVID-19-related variables. Data were analyzed using Poisson regression with robust variance[26] to estimate the prevalence ratio (PR) and the respective 95% CI of the factors associated with sleep quality. Independent variables that had an association at a P value of 0.2 were used in multivariate regression with a stepwise backward elimination procedure controlling for the pandemic period variable. Collinearity among covariates was examined by calculating the variance inflation factor. The variables of anxiety and self-rated health were collinear and opted to retain anxiety disorders in the final model.

In addition, bivariate analysis was performed on the multivariate model of the interaction between the associated factors to verify a possible effect modification on sleep quality.

RESULTS

Characteristics and sleep quality of participants

Among the participants, women reported a high prevalence of abnormal PSQI scores in the subdomains of subjective sleep quality, sleep efficiency, and the use of sleep medications (P < 0.05). Furthermore, sleep medication use increased with increasing age, and daytime dysfunction was higher in the younger age group (P < 0.05) (**Table 1**). The mean PSQI score was 6.32 (95% CI: 6.03–6.62), and the prevalence of poor sleep quality was 52.5%. The highest prevalence rates for the abnormal specific sleep domains were for sleep latency (45.8%), sleep disturbance (36.8%), and sleep efficiency (20.1%) (see supplementary data: Figure S1 available in Google Drive: https://drive.google.com/file/d/1i0-Nvn6kRC4idX2rvWl0uDVWrSfwRKhI/view?usp=sharing).

Among the participants, 51.9% were women, and the most prevalent age group was 35–59 years (45.6%). Most participants were married (53.2%), had > 9 years of schooling (68.8%), and had a family income ≤ 2 times the minimum wage (41.1%) (**Table 2**). More than half of the participants had at least one chronic disease (52.3%), consumed alcoholic beverages (58.2%), were physically inactive (69.2%), and were overweight (61.4%) (**Table 3**). At least 12% of the participants experienced 5.0% weight loss or gain during the pandemic (12.4% and 17.7%, respectively), 35.0% had a daily sun exposure of < 30 minutes, and 27.1% had vitamin D deficiency (**Table 4**).

Factors associated with poor sleep quality

In the multivariate model, the following factors were significantly associated with poor sleep quality: living alone (PR = 1.34; 95% CI: 1.04–1.73), anxiety disorder (PR = 1.32; 95% CI: 1.08–1.62), 5.0% weight loss (PR = 1.21; 95% CI: 1.02–1.44), 5.0% weight gain (PR = 1.27; 95% CI: 1.03–1.55), vitamin D deficiency (PR = 1.16;

Table 1. Distributions of abnormal Pittsburgh Sleep Quality Index subdomains by sleep quality, age and sex

	Abnormal Pittsburgh Sleep Quality Index subdomains[a], n (%)						
	Subjective sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbance	Use of sleep medications	Daytime dysfunction
Total sample	18.3 (14.9–22.4)	45.8 (41.6–50.1)	15.7 (12.3–19.8)	20.1 (16.7–24.1)	36.8 (32.0–41.9)	9.6 (7.6–12.1)	13.9 (11.0–17.5)
Sex							
Male	36.6 (27.2–47.2)	43.8 (34.6–53.5)	44.3 (35.2–53.7)	37.5 (28.7–47.1)	42.8 (32.9–53.2)	29.0 (19.9–40.3)	39.8 (27.7–53.3)
Female	63.4 (52.8–72.8)	56.2 (46.5–65.4)	55.7 (46.3–64.8)	62.5 (52.9–71.3)	57.2 (46.8–67.1)	71.0 (59.7–80.1)	60.2 (46.7–72.3)
P value	**0.043**	0.108	0.448	**0.032**	0.070	**0.001**	0.222
Age							
18–34 years	35.6 (25.6–47.7)	36.0 (29.0–43.6)	33.7 (22.0–47.8)	31.7 (22.4–42.8)	28.8 (21.0–38.1)	11.1 (5.6–20.9)	50.2 (38.0–62.3)
35–59 years	47.0 (35.3–59.0)	45.3 (37.2–53.7)	44.8 (32.4–57.8)	44.8 (36.8–53.0)	48.2 (37.7–58.9)	54.4 (43.2–65.1)	35.0 (25.2–46.3)
≥ 60 years	17.1 (12.4–23.1)	18.7 (14.9–23.0)	21.5 (15.2–29.6)	23.5 (18.1–30.0)	23.0 (17.0–30.2)	34.5 (24.8–45.5)	14.8 (9.7–21.9)
P value	0.854	0.971	0.746	0.385	0.157	**< 0.001**	**0.004**

[a]Score for each domain ranges from 0 to 3 (no difficulty to severe difficulty), and a domain score ≥ 2 indicates abnormal sleep in the domain.

Table 2. Sociodemographic characteristics according to sleep quality during pandemic

Characteristics	Total % (95% CI)	Sleep quality		*Prevalence ratio* (95% CI)	P*
		Good (PSQI ≤ 5) % (95% CI)	Poor (PSQI > 5) % (95% CI)		
Total		**47.5 (43.6–51.4)**	**52.5 (48.6–56.4)**	-	-
Sociodemographic					
Sex					
Male	48.1 (41.0–55.2)	47.2 (39.3–55.2)	43.8 (36.2–51.7)	1.00	
Female	51.9 (44.7–59.0)	52.8 (44.8–60.7)	56.2 (48.3–63.8)	*1.20 (1.05–1.36)*	*0.006*
Age					
18–34 years	35.6 (31.1–40.3)	38.7 (30.5–47.6)	32.8 (26.4–39.9)	1.00	
35–59 years	45.6 (41.1–50.2)	44.5 (37.0–52.3)	46.6 (38.8–54.5)	*1.11 (0.82–1.49)*	*0.496*
≥ 60 years	18.8 (15.5–22.7)	16.8 (12.4–22.3)	20.6 (16.4–25.7)	*1.22 (0.94–1.58)*	*0.122*
Marital status					
Married	53.2 (47.2–59.2)	58.0 (51.2–64.6)	48.9 (40.8–57.1)	1.00	
Unmarried	46.8 (40.8–52.8)	42.0 (35.4–48.8)	51.1 (42.8–59.2)	*1.17 (0.97–1.40)*	*0.091*
Living status					
Non-alone	95.3 (93.5–96.6)	97.5 (96.4–98.2)	99.3 (90.1–95.5)	1.00	
Alone	4.7 (3.4–6.5)	2.5 (1.7–3.6)	6.7 (4.5–9.9)	*1.44 (1.24–1.68)*	*< 0.001*
Education					
> 9 years	68.8 (64.0–73.3)	75.7 (69.1–81.2)	62.6 (54.5–70.1)	1.00	
≤ 9 years	31.2 (26.7–36.0)	24.3 (18.8–30.9)	37.4 (29.9–45.5)	*1.33 (1.09–1.64)*	*0.006*
Family Income					
≤ 2 MW	41.1 (35.6–46.8)	38.9 (30.4–48.0)	43.0 (34.0–52.5)	1.00	
> 2 to ≤ 4 MW	32.0 (26.9–37.5)	31.4 (24.6–39.1)	32.5 (26.2–39.5)	*0.99 (0.76–1.29)*	*0.955*
> 4 MW	26.9 (22.0–32.5)	29.7 (21.4–39.7)	24.5 (18.3–31.9)	*0.86 (0.60–1.24)*	*0.428*
Workers					
No	47.5 (42.7–52.3)	44.2 (36.5–52.2)	50.5 (43.2–57.8)	1.00	
Yes	52.5 (47.7–57.3)	55.8 (47.8–63.5)	49.5 (42.2–56.8)	*0.89 (0.71–1.11)*	*0.299*
Work from home[a]					
No	61.4 (53.5–68.8)	57.6 (57.4–76.3)	55.0 (44.9–64.7)	1.00	
Yes	38.6 (31.2–46.5)	32.4 (23.7–42.6)	45.0 (35.3–55.1)	*1.30 (0.99–1.71)*	*0.056*
Shift work					
No	91.4 (86.3–94.7)	89.4 (78.1–95.3)	93.2 (88.6–96.1)	1.00	
Yes	8.6 (5.3–13.7)	10.6 (4.7–21.9)	6.8 (3.9–11.4)	*0.77 (0.41–1.43)*	*0.405*

PSQI = Pittsburgh Sleep Quality Index; MW = Minimum wage; CI = confidence interval.

[a]Percentage of active workers who were working at home.

Prevalence ratio estimated by Poisson regression with robust variance.

*In order to avoid the type 1 error, the Bonferroni correction for multiple [9] tests, was set at 0.005.

95% CI: 1.01–1.35), and COVID-19 symptoms (PR = 1.29; 95% CI: 1.10–1.52).

Based on the factors associated with sleep quality obtained in the aforementioned adjusted model (**Table 5**), a chance modification analysis for poor sleep quality was performed, assuming the presence of combined changes in these variables (**Figure 1**). Overall, we observed that the assessed variables had a gradient of probability for sleep quality, with the PR of poor sleep quality increasing when two concurrently altered variables were analyzed. The worst scenarios were the concurrence of COVID-19 symptoms and weight loss (PR = 1.72; 95% CI: 1.38–2.15) and vitamin D deficiency and weight gain (PR = 1.67; 95% CI: 1.19–1.91). Only weight loss when evaluated concomitantly with vitamin D deficiency was not significant (PR = 1.09; 95% CI: 0.73–1.62).

DISCUSSION

This study investigated the prevalence of poor sleep quality and its associated factors during the COVID-19 pandemic. More than half of the population had poor sleep quality. The PR of poor sleep quality was higher in individuals living alone, with anxiety disorders, experiencing weight change during the pandemic, with vitamin D deficiency, and with COVID-19 symptoms. The most affected PSQI sub-domains were sleep latency, sleep disturbance, and sleep efficiency.

During the pandemic, several factors may have contributed to the alteration of normal sleep architecture. Hence, population studies are important because they allow us to evaluate how health outcomes affect people's lives. However, only a few studies with

Table 3. Health conditions according to sleep quality during pandemic

Characteristics	Total	Sleep quality		*Prevalence ratio* (95% CI)	P*
		Good (PSQI ≤ 5) % (95% CI)	Poor (PSQI > 5) % (95% CI)		
Health conditions					
Chronic diseases					
No	47.7 (41.3–54.2)	52.9 (44.1–61.5)	43.0 (35.8–50.5)	1.00	
Yes	52.3 (45.8–58.7)	47.1 (38.5–55.9)	57.0 (49.4–64.2)	*1.22 (1.10–1.35)*	*< 0.001*
Chronic pain					
No	65.7 (61.4–69.7)	75.0 (66.9–81.7)	57.3 (49.5–64.7)	1.00	
Yes	34.3 (30.3–38.6)	25.0 (18.3–33.1)	42.7 (35.3–50.5)	*1.44 (1.13–1.83)*	*0.004*
Healthcare[a]					
Anxiety disorder	20.6 (17.0–24.8)	12.8 (7.6–20.8)	27.7 (22.9–33.1)	*1.49 (1.22–1.83)*	*< 0.001*
Depression	12.7 (9.6-16.6)	7.0 (3.0–15.8)	17.9 (14.1–22.4)	*1.52 (1.17–1.97)*	*0.002*
Self-rated health					
Good	77.4 (73.3–80.9)	87.5 (83.9–90.3)	68.2 (61.7–74.1)	1.00	
Poor	22.6 (19.0–26.7)	12.5 (9.7–16.1)	31.8 (25.9–38.3)	*1.62 (1.42–1.83)*	*< 0.001*
Behaviors					
Current smoking	17.0 (13.3–21.4)	18.3 (12.6–25.9)	15.8 (11.3–21.5)	*0.90 (0.66–1.22)*	*0.508*
Current alcohol consumption	58.2 (52.1–64.0)	62.2 (55.9–68.2)	54.5 (46.8–62.1)	*1.15 (0.89–1.33)*	*0.053*
Physical activity					
Physically active	30.8 (26.2–35.8)	35.1 (28.2–42.5)	26.9 (21.2–33.5)	1.00	
Physically inactive	69.2 (64.2–73.7)	64.9 (57.5–71.8)	73.1 (66.5–78.8)	*1.22 (0.96–1.55)*	*0.096*
Nutritional status					
Eutrophic	36.0 (30.7–41.7)	34.5 (27.7–42.1)	37.4 (29.8–45.7)	1.00	
Underweight	2.6 (1.8–3.6)	2.4 (1.5–3.8)	2.7 (1.6–4.4)	*1.02 (0.73–1.43)*	*0.918*
Overweight	61.4 (55.6–66.9)	63.0 (55.4–70.0)	59.9 (51.6–67.7)	*0.95 (0.76–1.19)*	*0.676*

PSQI = Pittsburgh Sleep Quality Index; CI = confidence interval.

[a]Anxiety disorder and depression (evaluated by self-report of medical diagnosis).

Prevalence ratio estimated by Poisson regression with robust variance.

*In order to avoid the type 1 error, the Bonferroni correction for multiple [7] tests, was set at 0.007.

this methodology using the PSQI have been conducted during the pandemic, which makes it difficult to compare the results. Our study, conducted from October to December 2020, reported a higher prevalence of poor sleep quality than studies conducted at the beginning of the pandemic, such as the systematic review by Krishnamoorthy et al. (2020), wherein, approximately 36% of the general population and 43% of healthcare workers, which were one of the most affected groups during the pandemic, reported poor sleep quality.[27]

Furthermore, a multicenter online survey conducted from April to May 2020 corroborates our results. In that survey, 5,056 individuals from Europe, North Africa, West Asia, and the Americas were evaluated, and a 52.0% prevalence of poor sleep quality was assessed using the PSQI.[28] In Brazil, a study on 45,161 individuals from April to May 2020 showed that during the pandemic, 66.1% reported usual sleep problems. This was particularly noted in women aged 40–50 years, unemployed and physically inactive individuals, and those with a greater number of health problems.[29] However, it should be noted that this study was conducted online, which would usually represent a more educated and higher-income group of the population and hence is different from a household survey.

During the pandemic, online tasks made the workday endless and affected sleep quality. Such a work schedule also reduced individuals' sun exposure, as most people spending more time doing online tasks no longer commuted to work or lunch. Sun exposure is an important factor because it is the main source of endogenous vitamin D.[21] We found that individuals with insufficient vitamin D levels had a higher PR for poor sleep quality than those with sufficient levels. This association may be explained by the intracellular distribution of vitamin D receptors in brain areas that regulate the sleep-wake cycle or through pro-inflammatory mediators. Vitamin D is also involved in the production of melatonin, an essential hormone in the regulation of circadian rhythm and sleep. Melatonin synthesis is controlled by the active form of vitamin D, $1,25(OH)_2D$, that induces the expression of tryptophan hydroxylase (the initial enzyme in the melatonin synthesis pathway).[30] This suggests a possible role for vitamin D deficiency in sleep disturbances.[31,32] These results were found in a previous study on mining workers conducted in the same region as that of our study.

Table 4. Coronavirus disease 2019 (COVID-19) related variables according to sleep quality during pandemic

Characteristics	Total	Sleep quality		*Prevalence ratio* (95% CI)	P*
		Good (PSQI ≤ 5) % (95% CI)	Poor (PSQI > 5) % (95% CI)		
Weight change[a]					
Δ -5% to +5%	69.9 (64.8–74.5)	76.6 (71.6–80.9)	63.9 (56.5–70.8)	1.00	
Δ ≤ -5%	12.4 (9.3–16.4)	10.1 (7.3–13.7)	14.5 (9.7–21.0)	*1.27 (1.04–1.55)*	*0.022*
Δ ≥ +5%	17.7 (14.8–21.1)	13.3 (9.9–17.8)	21.6 (16.7–27.5)	*1.32 (1.09–1.59)*	*0.004*
Exposure sun					
≥ 30 minutes/day	64.5 (59.3–70.3)	69.1 (62.6–74.8)	61.3 (53.7–68.4)	1.00	
< 30 minutes/day	35.0 (29.7–40.7)	30.9 (25.1–37.4)	38.7 (31.6–46.3)	*1.16 (0.98–1.35)*	*0.074*
Vitamin D supplementation					
No	77.9 (73.3–81.9)	80.2 (74.6–84.8)	75.9 (69.4–81.4)	1.00	
Yes	22.1 (18.0–26.7)	19.8 (15.2–25.4)	24.1 (18.6–30.6)	*1.14 (0.93–1.40)*	*0.212*
Vitamin D scenario[b]					
Sufficient	72.9 (68.1–77.3)	76.7 (72.3–81.1)	69.3 (62.3–75.4)	1.00	
Insufficient	27.1 (22.7–31.9)	23.0 (18.9–27.7)	30.7 (24.5–37.7)	*1.19 (1.03–1.37)*	*0.020*
SARS-CoV-2					
Seronegative	94.8 (93.0–96.2)	94.9 (91.8–96.9)	94.7 (92.1–96.5)	1.00	
Seropositive	5.2 (3.8–7.0)	5.1 (3.1–8.2)	5.3 (3.5–7.9)	*1.12 (0.79–1.59)*	*0.518*
Symptoms of COVID-19					
No	71.4 (66.7–75.8)	79.8 (75.0–83.8)	63.8 (56.7–70.4)	1.00	
Yes	28.6 (24.2–33.3)	20.2 (16.2–25.0)	36.2 (29.6–43.3)	*1.44 (1.24–1.65)*	*< 0.001*
Risk group in family					
No	40.8 (33.8–48.2)	46.2 (38.8–53.7)	36.0 (28.2–44.5)	1.00	
Yes	59.2 (51.8–66.2)	53.8 (46.3–61.2)	64.0 (55.5–71.8)	*1.23 (1.07–1.42)*	*0.003*
Pandemic period					
8.5–9 months	18.9 (14.6–24.1)	22.5 (16.6–29.6)	15.6 (11.7–20.6)	1.00	
7–8.4 months	81.1 (75.9–85.4)	77.5 (70.4–83.3)	84.4 (79.4–88.3)	*1.26 (1.04–1.53)*	*0.018*
Daily routine in pandemic					
Social contact restriction	62.6 (58.3–66.7)	56.7 (48.3–64.7)	68.0 (61.3–73.9)	*1.28 (0.98–1.66)*	*0.069*
Physical activity in the street	23.9 (20.3–28.0)	26.1 (18.8–34.9)	22.0 (18.1–26.5)	*0.90 (0.68–1.18)*	*0.428*
Physical activity in the gym	10.2 (6.7–15.2)	14.2 (8.5–22.6)	6.6 (3.7–11.4)	*0.62 (0.37–1.01)*	*0.058*

PSQI = Pittsburgh Sleep Quality Index; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a]Weight change during the pandemic (self-reported weight).

[b]Sufficient: Sun exposure > 30 minutes/day or vitamin D supplements; Insufficient: Sun exposure < 30 minutes/day and no vitamin D supplements.

Prevalence ratio estimated by Poisson regression with robust variance.

*In order to avoid the type 1 error, the Bonferroni correction for multiple [9] tests, was set at 0.005.

When evaluating sleep quality using polysomnography, the gold standard method, workers with hypovitaminosis D had more sleep disturbances than those without it.[33] The routine of these workers was similar to that of people confined during the COVID-19 pandemic, since they were off-road machinery drivers who spent most of their time on machines without access to sunlight.[34]

An additional variable associated with poor sleep quality in our study was weight change during the pandemic. Individuals who reduced or gained up to 5.0% of their body weight during the pandemic had a greater PR for poor sleep quality than those who did not experience weight change. Weight loss, when intentional, particularly in obese individuals, can be beneficial in improving sleep quality.[35] However, unintentional weight loss may be related to increased physical and emotional stress or an imbalance between food supply and demand. A systematic review conducted between July 2020 and February 2021 found that during the pandemic, 11.1–32.0% of the total 469,362 participants had experienced weight loss.[36] For some people, the lockdown provided more time to cook and eat better; however, most people developed malnutrition and experienced weight loss owing to inflated food prices and food insecurity. In Brazil, more than half of the households (59.4%) experienced food insecurity during the pandemic.[37] Insufficient food consumption of adequate quantity and quality can have severe health effects, such as poor mental health and increased likelihood of diseases,[37] increasing the chances of poor sleep quality and vulnerability to COVID-19.

In addition, pandemic confinement was associated with weight gain in 7.2–72.4% of participants in a previous systematic review.[36]

Table 5. Multivariate analysis of factors associated with poor sleep quality

Variables	Univariate analysis			Multivariate analysis		
	PR	95% CI	P	PR	95% CI	P
Living status						
Non-alone	1.00	-		1.00	-	
Alone	*1.44*	*1.24–1.68*	***< 0.001***	*1.34*	*1.04–1.73*	***0.026***
Anxiety disorder[a]						
No	1.00	-		1.00	-	
Yes	*1.49*	*1.22–1.83*	***< 0.001***	*1.32*	*1.08–1.62*	***0.008***
Weight change[b]						
Δ -5% to +5%	1.00	-		1.00	-	
Δ ≤ -5%	*1.27*	*1.04–1.55*	***0.022***	*1.21*	*1.02–1.44*	***0.028***
Δ ≥ +5%	*1.32*	*1.09–1.59*	***0.004***	*1.27*	*1.03–1.55*	***0.026***
Vitamin D scenario[c]						
Sufficient	1.00	-		1.00	-	
Insufficient	*1.19*	*1.03–1.37*	***0.020***	*1.16*	*1.01–1.35*	***0.043***
Symptoms of COVID-19						
No	1.00	-		1.00	-	
Yes	*1.43*	*1.24–1.65*	***< 0.001***	*1.29*	*1.10–1.52*	***0.003***

Multivariate model adjusted for the best fit model, by the technique stepwise backward. Model included sex, age, living status, anxiety, weight change, vitamin D scenario, symptoms of coronavirus disease (COVID) and pandemic period.

[a]Anxiety disorder and depression (evaluated by self-report of medical diagnosis).

[b]Weight change during the pandemic (self-reported weight).

[c]Sufficient: Sun exposure > 30 min/day or vitamin D supplements; Insufficient: Sun exposure < 30 minutes/day and no vitamin D supplements.

CI = confidence interval; PR = prevalence ratio; COVID-19 = coronavirus disease 2019.

Prevalence ratio estimated by Poisson regression with robust variance.

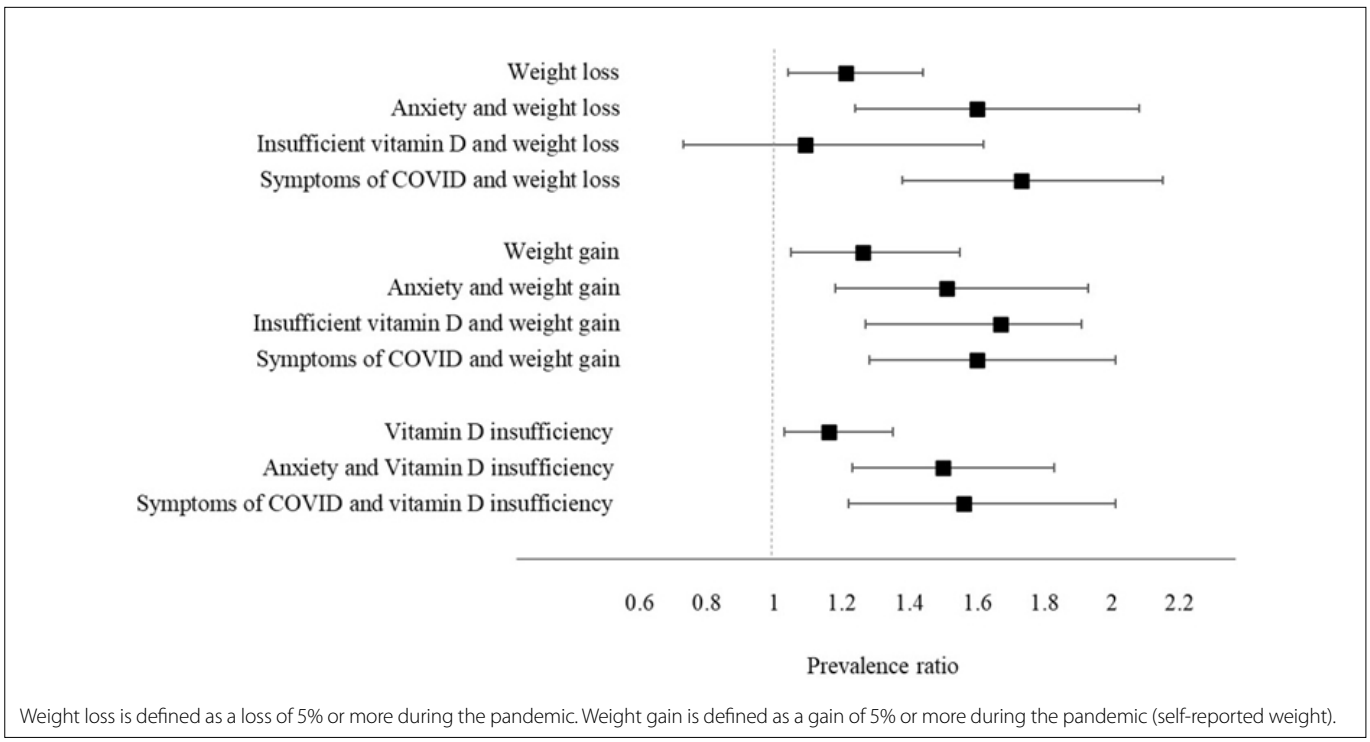


Figure 1. Bivariate association adjusted for weight change, and vitamin D scenario insufficiency with individual parameters associated with poor sleep quality during the COVID-19 pandemic.

Excess weight interferes with sleep quality in several aspects, including anatomical factors such as airway obstruction or inflammatory factors such as increased cytokines, which can induce sleep disturbances by altering the sleep-wake rhythm.[38] Furthermore, there is a strong association between poor sleep quality and the risk of obesity, as demonstrated in previous longitudinal studies. In a cohort of 83,377 Americans, comprising non-obese men and women at baseline, participants reporting < 5 hours of sleep per night had an approximately 40% higher risk of developing obesity than those reporting 7–8 hours of sleep (for men, odds ratio [OR] = 1.45, 95% CI: 1.06–1.99; for women, OR = 1.37, 95% CI: 1.04–1.79).[39] Furthermore, a recent study evaluating sleep disturbances in 4,384 health professionals during COVID-19 found that weight loss or weight gain were independent predictors of new-onset or worsening of preexisting insomnia (for weight loss, OR = 1,772, 95% CI: 1,453–2,161; for weight gain, OR = 1,468; 95% CI: 1,249–1,728).[40]

Unfortunately, the fear and uncertainty caused by the pandemic and threat to survival, among other factors, are some of the main problems encountered during the pandemic that have greatly influenced the quality of life and mental health.[4] Of all the factors evaluated in our study, anxiety and living alone were the most strongly associated with poor sleep quality.

Pandemic conditions and social isolation affect many aspects of living conditions and the health status of the population, particularly mental health. In Brazil, 52.6% of the population reported frequently feeling anxious or nervous.[6] Anxiety, especially generalized anxiety disorder, has been described as one of the most important consequences of sleep deprivation.[41] A study conducted during the initial weeks of the lockdown in Italy showed that reduced sleep quality was directly related to the days spent at home in confinement, as mental health plays an important role in mediating sleep quality.[42] A systematic review and meta-analysis of 345,270 participants from 39 countries showed consistent results regarding the association between sleep quality and psychological distress. The corrected pooled estimated prevalence of sleep problems was 18% in the general population and was positively associated with anxiety (Fisher z-score = 0.48; 95% CI: 0.41–0.54).[41]

The psychological impact during a pandemic is common and expected, as demonstrated by Brooks et al. (2020), who studied previous epidemics. The main psychological stressors were duration of quarantine, fear of infection, feelings of frustration and annoyance, inadequate information about disease precautions, unemployment, financial losses, and stigma associated with the disease.[4]

In addition to these factors, we also found that participants who experienced co-occurrence of two associated factors had a higher PR for poor sleep quality than those who did not. These results are important because the social and health effects of the pandemic have rendered many individuals vulnerable to the co-occurrence of factors that negatively interfere with sleep quality. In this context, vitamin D deficiency and weight gain are closely related factors that can occur simultaneously.[21,31] Therefore, the co-occurrence of these factors can increase the PR of poor sleep quality, as shown in this study. To the best of our knowledge, this is the first study to evaluate the co-occurrence of the factors associated with poor sleep quality during the COVID-19 pandemic.

Insufficient sleep directly affects the immune system and increases the risk for illness. Thus, we found a high prevalence of poor sleep quality during the COVID-19 pandemic, with several associated factors. Sleep quality may have been influenced by the COVID-19 pandemic and the government's actions taken to contain it. Brazil is one of the countries with the highest number of deaths and the lowest percentage of vaccinated individuals.

Adequate sleep quality is an important factor to consider in a pandemic, given its beneficial effect on numerous health conditions and improvement of the immune response against opportunistic infections.[1] Thus, a health-related emergency, such as the one we are currently experiencing, should be accompanied by adequate social support programs to mitigate the psychological, social, and economic effects and promote better circumstances to face such troubled times.

This study identified the important factors related to sleep quality during the pandemic; however, these findings should be interpreted with caution. In our study, causal relationships could not be determined because of the absence of previously available information on sleep quality. Furthermore, the variables were obtained by self-reporting, which may have caused underestimation of risk or overestimation of protective behaviors owing to differences in each individual's perception of the pandemic and associated factors. However, the assessment of sleep quality needs to be performed subjectively since it considers the factors intrinsic to individuals' perception of their sleep. Self-reported weight and height may have influenced these results; however, there are studies involving similar populations and strong methodological rigor that demonstrated high agreement with the measured values.[43,44] Therefore, BMI computed from self-reported weight and height can be considered a valid measure in men and women of different sociodemographic groups.[43,44] The strengths of this study include a representative random sample of the resident population from different socioeconomic strata, evaluation using a household survey, and face-to-face interviews during the COVID-19 pandemic, which increased the robustness of the study.

CONCLUSION

Our study revealed that more than half of the participants had poor sleep quality during the COVID-19 pandemic. Moreover, factors associated with poor sleep quality were related to the pandemic, such as vitamin D deficiency and weight change.

Therefore, future longitudinal and randomized intervention trials should be conducted to confirm the relevant associations. Thus, governing and regulatory bodies must provide subsidies for decision-making in chaotic socio-sanitary and epidemiological conditions to reduce the worsening of health conditions.

REFERENCES

1. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol. 2015;66:143-72. PMID: 25061767; https://doi.org/10.1146/annurev-psych-010213-115205.
2. Benedict C, Cedernaes J. Could a good night's sleep improve COVID-19 vaccine efficacy? Lancet Respir Med. 2021;9(5):447-8. PMID: 33721558; https://doi.org/10.1016/S2213-2600(21)00126-0.
3. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus Pandemic (COVID-19). Available from: https://ourworldindata.org/coronavirus. Accessed in 2022 (Aug 25).
4. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912-20. PMID: 32112714; https://doi.org/10.1016/S0140-6736(20)30460-8.
5. Di Renzo L, Gualtieri P, Pivari F, et al. Eating habits and lifestyle changes during COVID-19 lockdown: an Italian survey. J Transl Med. 2020;18(1):229. PMID: 32513197; https://doi.org/10.1186/s12967-020-02399-5.
6. Barros MBA, Lima MG, Malta DC, et al. Report on sadness/depression, nervousness/anxiety and sleep problems in the Brazilian adult population during the COVID-19 pandemic. Epidemiol Serv Saude. 2020;29(4):e2020427. PMID: 32844918. https://doi.org/10.1590/s1679-49742020000400018.
7. Lancel M, Boersma GJ, Kamphuis J. Insomnia disorder and its reciprocal relation with psychopathology. Curr Opin Psychol. 2021;41:34-9. PMID: 33691218; https://doi.org/10.1016/j.copsyc.2021.02.001.
8. Pérez-Rodrigo C, Gianzo Citores M, Hervás Bárbara G, et al. Patterns of Change in Dietary Habits and Physical Activity during Lockdown in Spain Due to the COVID-19 Pandemic. Nutrients. 2021;13(2):300. PMID: 33494314; https://doi.org/10.3390/nu13020300.
9. Meireles AL, Lourenção LG, Menezes Junior LAA de, et al. COVID-Inconfidentes - SARS-CoV-2 seroprevalence in two Brazilian urban areas during the pandemic first wave: study protocol and initial results. SciELO Preprints. 2021. https://doi.org/10.1590/SciELOPreprints.2720.
10. World Health Organization. Guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147. Accessed in 2022 (Aug 25).
11. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1-452. PMID: 8594834.
12. Organização Pan-Americana de Saúde O. XXXVI Reunión del Comitê Asesor de Investigaciones en Salud. Washington, DC: OPAS; 2001.
13. de las Fuentes L, Waggoner AD, Mohammed BS, et al. Effect of moderate diet-induced weight loss and weight regain on cardiovascular structure and function. J Am Coll Cardiol. 2009;54(25):2376-81. PMID: 20082927; https://doi.org/10.1016/j.jacc.2009.07.054.
14. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(7):434-47. PMID: 21969342; https://doi.org/10.7326/0003-4819-155-7-20110040-00006.
15. Messier SP. Diet and exercise for obese adults with knee osteoarthritis. Clin Geriatr Med. 2010;26(3):461-77. Erratum in: Clin Geriatr Med. 2013;29(2):ix. PMID: 20699166; https://doi.org/10.1016/j.cger.2010.05.001.
16. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. Sleep Med. 2018;52:198-210. PMID: 30314881; https://doi.org/10.1016/j.sleep.2018.05.023.
17. Associação Brasileira para Estudo da Obesidade e Síndrome Metabólica. Atualização das diretrizes para o tratamento farmacológico da obesidade e do sobrepeso. ABESO. 2010;76:4-18. Available from: https://abeso.org.br/wp-content/uploads/2019/12/Atualizacao-das-Diretrizes.pdf. Accessed in 2022 (Aug 25).
18. Dietitians Association of Australia. DAA best practice guidelines for the treatment of overweight and obesity in adults. Report to inform the 2011 revision of the 2005 guidelines. 25 January 2012. Available from: https://www.pennutrition.com/resources/PEN_resources/DAA%20PDFs/FINAL-DAA-obesity-guidelines-report-25th-January-2011-2.pdf. Accessed in 2022 (Aug 25).
19. FDA. Guidance for industry: developing products for weight management. Rockville: Food and Drug Administration; 2007.
20. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: a report of the American College of Cardiology/American heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102-38. Erratum in: Circulation. 2014;129(25 Suppl 2):S139-40. PMID: 24222017; https://doi.org/10.1161/01.cir.0000437739.71477.ee.
21. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81. PMID: 17634462; https://doi.org/10.1056/NEJMra070553.
22. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213. PMID: 2748771; https://doi.org/10.1016/0165-1781(89)90047-7.
23. Bertolazi AN, Fagondes SC, Hoff LS, et al. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. Sleep Med. 2011;12(1):70-5. PMID: 21145786; https://doi.org/10.1016/j.sleep.2010.04.020.
24. Wang P, Song L, Wang K, et al. Prevalence and associated factors of poor sleep quality among Chinese older adults living in a rural area: a population-based study. Aging Clin Exp Res. 2020;32(1):125-31. PMID: 30919262; https://doi.org/10.1007/s40520-019-01171-0.

25. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ. 1995;310(6973):170. PMID: 7833759; https://doi.org/10.1136/bmj.310.6973.170.
26. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003;3:21. PMID: 14567763; https://doi.org/10.1186/1471-2288-3-21.
27. Krishnamoorthy Y, Nagarajan R, Saya GK, Menon V. Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: A systematic review and meta-analysis. Psychiatry Res. 2020;293:113382. PMID: 32829073; https://doi.org/10.1016/j.psychres.2020.113382.
28. Trabelsi K, Ammar A, Masmoudi L, et al. Globally altered sleep patterns and physical activity levels by confinement in 5056 individuals: ECLB COVID-19 international online survey. Biol Sport. 2021;38(4):495-506. PMID: 34937958; https://doi.org/10.5114/biolsport.2021.101605.
29. Szwarcwald CL, Damacena GN, Barros MBA, et al. Factors affecting Brazilians' self-rated health during the COVID-19 pandemic. Cad Saude Publica. 2021;37(3):e00182720. PMID: 33950075; https://doi.org/10.1590/0102-311X00182720.
30. Romano F, Muscogiuri G, Di Benedetto E, et al. Vitamin D and Sleep Regulation: Is there a Role for Vitamin D? Curr Pharm Des. 2020;26(21):2492-6. PMID: 32156230; https://doi.org/10.2174/1381612826666200310145935.
31. Bellia A, Garcovich C, D'Adamo M, et al. Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med. 2013;8(1):33-40. PMID: 21437585; https://doi.org/10.1007/s11739-011-0559-x.
32. Gao Q, Kou T, Zhuang B, et al. The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. Nutrients. 2018;10(10):1395. PMID: 30275418; https://doi.org/10.3390/nu10101395.
33. Menezes-Júnior LAA de, Fajardo VC, Freitas SN de, et al. Hypovitaminosis D is associated with sleep disorders in workers on alternating shifts with cardiovascular risk factors. medRxiv. 2021. https://doi.org/10.1101/2021.05.04.21256625.
34. de Menezes Júnior LAA, Fajardo VC, do Nascimento Neto RM, et al. Diagnostic accuracy of the Berlin questionnaire and the NoSAS score in detecting risk for obstructive sleep apnea in rotating shift workers. Sleep Breath. 2022;26(2):743-51. PMID: 34338952; https://doi.org/10.1007/s11325-021-02446-5.
35. Hargens TA, Kaleth AS, Edwards ES, Butner KL. Association between sleep disorders, obesity, and exercise: a review. Nat Sci Sleep. 2013;5:27-35. PMID: 23620691; https://doi.org/10.2147/NSS.S34838.
36. Khan MAB, Menon P, Govender R, et al. Systematic review of the effects of pandemic confinements on body weight and their determinants. Br J Nutr. 2022;127(2):298-317. PMID: 33706844; https://doi.org/10.1017/S0007114521000921.
37. Galindo E, Teixeira MA, de Araújo M, et al. Efeitos da pandemia na alimentação e na situação da segurança alimentar no Brasil. Freie Universität Berlin. 2021. Available from: https://refubium.fu-berlin.de/handle/fub188/29813. Accessed in 2022 (Aug 25).
38. Muscogiuri G, Barrea L, Annunziata G, et al. Obesity and sleep disturbance: the chicken or the egg? Crit Rev Food Sci Nutr. 2019;59(13):2158-65. PMID: 30335476; https://doi.org/10.1080/10408398.2018.1506979.
39. Xiao Q, Arem H, Moore SC, Hollenbeck AR, Matthews CE. A large prospective investigation of sleep duration, weight change, and obesity in the NIH-AARP Diet and Health Study cohort. Am J Epidemiol. 2013;178(11):1600-10. PMID: 24049160; https://doi.org/10.1093/aje/kwt180.
40. Drager LF, Pachito DV, Moreno CRC, et al. Insomnia episodes, new-onset pharmacological treatments, and other sleep disturbances during the COVID-19 pandemic: a nationwide cross-sectional study in Brazilian health care professionals. J Clin Sleep Med. 2022;18(2):373-82. PMID: 34314346; https://doi.org/10.5664/jcsm.9570.
41. Alimoradi Z, Broström A, Tsang HWH, et al. Sleep problems during COVID-19 pandemic and its' association to psychological distress: A systematic review and meta-analysis. EClinicalMedicine. 2021;36:100916. PMID: 34131640; https://doi.org/10.1016/j.eclinm.2021.100916.
42. Casagrande M, Forte G, Tambelli R, Favieri F. The Coronavirus Pandemic: A Possible Model of the Direct and Indirect Impact of the Pandemic on Sleep Quality in Italians. Nat Sci Sleep. 2021;13:191-9. PMID: 33623460; https://doi.org/10.2147/NSS.S285854.
43. Hodge JM, Shah R, McCullough ML, Gapstur SM, Patel AV. Validation of self-reported height and weight in a large, nationwide cohort of U.S. adults. PLoS One. 2020;15(4):e0231229. PMID: 32282816; https://doi.org/10.1371/journal.pone.0231229.
44. Moreira NF, Luz VG, Moreira CC, et al. Self-reported weight and height are valid measures to determine weight status: results from the Brazilian National Health Survey (PNS 2013). Cad Saude Publica. 2018;34(5):e00063917. PMID: 29768583; https://doi.org/10.1590/0102-311X00063917.

Authors' contributions: Menezes-Junior LAAM: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal) and writing-original draft (equal); Lourenção LG: conceptualization (equal), data curation (equal), investigation (equal), methodology (equal), project administration (equal) and writing-review and editing (equal); Andrade ACS: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal) and writing-review and editing (equal); Carraro JCC: conceptualization (equal), data curation (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal) and writing-review and editing (equal); Machado-Coelho GLL: conceptualization (equal), data curation (equal), funding acquisition (equal), investigation (equal), methodology (equal),

project administration (equal) and writing-review and editing (equal); Meireles AL: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), supervision (equal) and writing-review and editing (equal). All the authors approved the submitted version

Acknowledgements: The authors acknowledge the Universidade Federal de Ouro Preto (UFOP) and the Grupo de Pesquisa em Nutrição e Saúde Coletiva (GPENSC) for their support and incentive and the support from the Municipal Health Secretariats of the municipalities evaluated in this study

Sources of funding: This study was supported by the Conselho Brasileiro de Desenvolvimento Científico e Tecnológico (CNPq), Distrito Federal, Brazil, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brazil (CAPES) [grant number 88887.504994/2020-00] and finance code 001 for PhD student scholarships
Conflicts of interest: The authors declare no conflicts of interest

Date of first submission: March 11, 2022
Last received: May 20, 2022
Accepted: August 19, 2022

Address for correspondence:
Adriana Lúcia Meireles
Faculdade de Nutrição, Universidade Federal de Ouro Preto (UFOP)
Campus Universitário, s/nº
Morro do Cruzeiro — Ouro Preto (MG) — Brasil
CEP: 35400-000
Tel. (+55 31) 3559-1828
E-mail: adriana.meireles@ufop.edu.br

Are sociodemographic and anthropometric variables effective in screening probable and confirmed sarcopenia in community-dwelling older adults? A cross-sectional study

Larissa Franciny de Souza[I], Laís Coan Fontanela[II], Amanda Aparecida Oliveira Leopoldino[III], Vanessa Amaral Mendonça[IV], Ana Lúcia Danielewicz[V], Ana Cristina Rodrigues Lacerda[VI], Núbia Carelli Pereira de Avelar[VII]

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

[I]PT. Physical Therapist, Department of Health Sciences, Universidade Federal de Santa Catarina (UFSC), Araranguá (SC), Brazil.
https://orcid.org/0000-0002-1194-1135

[II]PT. Physical Therapist, Department of Health Sciences, Universidade Federal de Santa Catarina (UFSC), Araranguá (SC), Brazil.
https://orcid.org/0000-0002-9058-2758

[III]PT, MSc, PhD. Adjunct Professor, Postgraduate Program, Faculdade de Ciências Médicas de Minas Gerais (FCM-MG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-3958-7107

[IV]PT, MSc, PhD. Associate Professor, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina (MG), Brazil.
https://orcid.org/0000-0002-1696-6091

[V]PT, MSc, PhD. Adjunct Professor, Department of Health Sciences, Universidade Federal de Santa Catarina (UFSC), Araranguá (SC), Brazil.
https://orcid.org/0000-0003-1563-0470

[VI]PT, MSc, PhD. Associate Professor, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina (MG), Brazil.
https://orcid.org/0000-0001-5366-3754

[VII]PT, MSc, PhD. Adjunct Professor, Department of Health Sciences, Universidade Federal de Santa Catarina (UFSC), Araranguá (SC), Brazil.
https://orcid.org/0000-0003-4212-4039

KEY WORDS (MeSH terms):
Sarcopenia.
Anthropometry.
Early diagnosis.
Aging.

AUTHORS' KEY WORDS:
Body weights and measures.
Early detection of disease.
Senescence.

ABSTRACT

BACKGROUND: Screening for probable and confirmed sarcopenia using sociodemographic and anthropometric indicators can be a practical, cheap, and effective strategy to identify and treat older people susceptible to this condition.

OBJECTIVES: To identify cutoff points for sociodemographic and anthropometric variables in screening probable and confirmed sarcopenia in community-dwelling older adults.

DESIGN AND SETTING: This was a cross-sectional study of community-dwelling older adults in Araranguá, Santa Catarina, Brazil.

METHODS: Sociodemographic (age, education) and anthropometric (weight, height, body mass index [BMI], waist circumference [WC], and dominant calf circumference [DCC]) factors were considered as predictors. The outcomes were probable sarcopenia (reduction in muscle strength assessed by time ≥ 15 s in the five-time sit-to-stand test) and confirmed sarcopenia (reduction in strength and muscle mass). Receiver operating characteristic curve analysis was used to analyze the ability to track sociodemographic and anthropometric variables for sarcopenia.

RESULTS: In 308 older adults, WC > 91 cm in women and age > 69 years in men were useful in screening for probable sarcopenia. The variables age, weight, BMI, WC, and DCC can be used to screen for sarcopenia in older women and men.

CONCLUSION: Sociodemographic and anthropometric variables are simple and accessible tools for sarcopenia screening in older adults.

INTRODUCTION

Sarcopenia is a condition resulting from a reduction in muscle strength, mass, and performance.[1] It is common in older adults and affects 10% of the older adult population worldwide,[2] as well as 17% of Brazilian older adults.[3] It is associated with negative health outcomes, such as increased mortality,[4] risk of falls,[5] functional disability,[6] and prolonged hospitalization time.[7]

The European Working Group on Sarcopenia in the Elderly (EWGSOP2)[1] proposed new diagnostic recommendations for early identification of this condition, in which the assessment should prioritize a reduction in muscle strength (classifying individuals with probable sarcopenia) using the five-time sit-to-stand test (5XSST) or handgrip strength (HGS) assessment.[1] In addition to the reduction in muscle strength, it is also necessary to quantify the decrease in muscle mass, which should primarily be performed using computed tomography, magnetic resonance imaging, dual energy radiological absorptiometry (DXA), or bioimpedance analysis, to confirm the diagnosis.[1] However, these assessments become unfeasible in clinical practice due to the high cost, risk of exposure to radiation, and low practicality.[1,8]

Underreporting of sarcopenia may occur in low- and middle-income countries that do not have easy access to these diagnostic tools, which cause the affected individuals to miss early intervention opportunities.[9] Therefore, evidence has suggested the use of anthropometric markers, such as body mass index (BMI), waist circumference (WC), and dominant calf circumference (DCC), to track sarcopenia.[10,12] Furthermore, Barbosa-Silva et al.[10] observed an association between confirmed sarcopenia and the variables education level and age, without establishing cutoff points for these variables. Although sociodemographic variables such as age are nonmodifiable risk

factors, access to cutoff points for screening sarcopenia can serve as a warning parameter for rehabilitation professionals. However, it is noteworthy that the diagnosis of sarcopenia in these studies was performed following the EWGSOP algorithm[13] suggested in 2010, in which sarcopenia was identified by the reduction in muscle mass, unlike what has been updated and proposed by EWGSOP2, in which sarcopenia is initially diagnosed by a reduction in muscle strength. Thus, it is necessary to define the cutoff points of these indicators in screening probable and confirmed sarcopenia considering the new definitions proposed by EWGSOP2.[1]

Esteves et al.[9] evaluated the use of anthropometric indicators in screening confirmed sarcopenia in older Brazilian adults using the EWGSOP2 algorithm.[1] However, screening for probable sarcopenia and the use of sociodemographic variables were not considered. Tracking the disease in its early stage (probable sarcopenia) is extremely relevant in clinical practice, since the reduction in muscle strength can lead to difficulties in performing activities of daily living, such as sitting and standing up from a chair, balance, and walking.[1]

Thus, no cutoff points have been identified to date for age and other sociodemographic and anthropometric indicators in screening for sarcopenia in community-dwelling older adults using the EWGSOP2 algorithm.[1]

OBJECTIVE

The aim of this study was to identify cutoff points in sociodemographic and anthropometric variables in screening probable and confirmed sarcopenia in community-dwelling older adults.

METHODS

Study design

This was a cross-sectional, household-based study with a probabilistic sample carried out in older adults from the municipality of Balneário Arroio do Silva, Santa Catarina, Brazil. Finite samples were calculated based on the total number of older adults registered (n = 2,833) in three basic health units (Unidade Básica de Saúde, UBS) of the city in 2018. An outcome prevalence of 50% was estimated with a five percentage point error (5 pp), and a 95% confidence interval (CI)[14] for a total sample of 308 older adults. However, considering the possible sample losses, 540 older adults were eligible to be included in the sample.

Population

Older adults were selected by drawing lots without replacement, considering the representative proportion of the total number of older adults registered in each UBS. Older people aged ≥ 60 years, who were residents of the community and able to perform 5XSST without the use of auxiliary devices were included in the study. Older adults who were bedridden and dependent, those who could not answer the questionnaires, residents in long-term care facilities, or those who had changed their residential addresses, were excluded. Losses were considered as older adults who were not found to be located at home after three attempts made on different days and times, and those who did not agree to participate in the study, and they were excluded. This study was approved by the Ethics Committee for Research with Human Beings of the Universidade Federal de Santa Catarina (UFSC) under the number CAAE no. 87776318.3.0000.0121 (dated June 22, 2018) and was conducted in accordance with the Declaration of Helsinki.

Data collection procedure

The data were collected between September 2018 and September 2019. The selected older adults were initially contacted by telephone, and visits to their homes were scheduled. The team of interviewers was trained with the study instruments.

Independent variables

The following sociodemographic variables were considered predictors: age (years) and education level (years of formal study), and anthropometric variables (body weight [kg], height [m], BMI, WC, and DCC).

During the assessment of body weight, older adults were instructed to wear a minimum amount of clothes and be barefoot. An anthropometric scale from the *Powner* brand was used with a capacity of up to 150 kg and a fraction of 100 g. Height was assessed after full inspiration with the spine supported on the wall, bare feet, and aligned.[15] Weight and height were considered for the assessment of BMI, which was obtained with the calculation suggested by the World Health Organization: "weight/height^2."[16]

A *Cescorf* brand inelastic tape was used to assess WC and DCC. WC was measured by marking the midpoint between the lower edge of the last rib and the upper edge of the iliac crest. For standardization purposes, DCC was measured with the older adults standing with their feet 20 cm apart in the region of maximum circumference in the plane perpendicular to the longitudinal line of the calf.[15]

Study outcomes

Probable and confirmed sarcopenia were considered as the study outcomes. The assessment of probable sarcopenia was performed using 5XSST, which measured the time taken to sit and stand up from a chair in five repetitions, with arms crossed over the chest.[17] Older adults who spent more than 15 s in the test were classified as probable sarcopenic.[1,18]

In addition to a reduction in muscle strength, older adults should also show a reduction in muscle mass to confirm sarcopenia.[1] Thus, the equation proposed by Lee et al.,[19] validated for

use in older Brazilian adults,[20] was used to assess the reduction in muscle mass. It presented a high correlation rate in the community-dwelling older adult population (r = 0.86 for women and r = 90 for men), in addition to high specificity (89%) and sensitivity (86%) when compared with the DXA method.[20]

Lee's Equation: SM (kg) = (0.244 * BW) + (7.8 * Ht) + (6.6 * gender) – (0.098 * age) + (race – 3.3)
where SM: skeletal muscle; BW: body weight (kg); Ht: height (m); gender: 1 for male and 0 for female; race: –1.2 for Asian, 1.4 for African American, and 0 for Caucasian or Hispanic.

After defining the skeletal muscle mass, the adjustment for height squared was performed, and the muscle mass index (MMI) was obtained.[20] The cutoff point used to identify muscle mass loss was the lowest 20% percentile of the population distribution.[21] In this study, MMI values < 6.700 kg/m^2 in women and < 9.60 kg/m^2 in men were considered confirmed sarcopenia, similar to the data found in the literature.[9]

Adjustment variables

After defining the cutoff points in screening sarcopenia, multivariate logistic regression analyses were performed to verify the association between the variables, considering the following adjustment variables: multimorbidity (concurrent presence of two or more self-reported chronic diseases),[22] depressive symptoms (a score ≥ 5 on the Geriatric Depression Scale),[23] level of leisure-time physical activity assessed by the International Physical Activity Questionnaire validated in Brazil[24,25] (categorized as sufficiently active [> 150 min] and insufficiently active [< 150 min])[26-28] and history of falls in the last 12 months.[29]

Data analysis

Data were collected and independently checked by two researchers and entered into the SPSS database (IBM, Chicago, Illinois, United States), version 23.0. The significance level adopted was 5%. Categorical variables were described using absolute and relative frequencies and their respective 95% CIs.

A receiver operating characteristic curve was constructed using the MedCalc software (MedCalc Software, Ostende, Belgium) version 19.1 to assess the ability to track sociodemographic and anthropometric variables for probable and confirmed sarcopenia. Multivariate logistic regression analyses were performed to assess the associations between variables and estimate the crude and adjusted odds ratios with 95% CIs.

RESULTS

Among the 540 eligible older adults, 64 were excluded from the study due to a change in address, 33 due to incomplete registrations, 29 due to refusal to participate, and 24 due to death, along with 82 losses, totaling 308 older adults evaluated in the study (**Figure 1**).

The sample consisted of 57.80% (178) older women, with a mean age of 69.91 ± 7.31 years and with 5.40 ± 3.64 years of schooling. Males accounted for 42.20% (130) of the sample, with a mean age of 69.80 ± 6.71 years and with 6.07 ± 3.83 years of formal education. The prevalence of probable sarcopenia was 50.60% in women and 38.30% in men, and that of confirmed sarcopenia was 6.80% in women and 8.10% in men. Sociodemographic and anthropometric variables of the participants are presented in **Table 1**.

The variable capable of tracking probable sarcopenia in older women was WC, with a cutoff point of > 91 cm. Age, formal education, weight, height, BMI, and DCC in women had no screening ability for probable sarcopenia (**Table 2**). The predictor variable for screening for probable sarcopenia in men was age, with a cutoff point of > 69 years. However, formal education, weight, height, BMI, WC, and DCC had no significant ability to track probable sarcopenia (**Table 2**).

For confirmed sarcopenia in women, the analysis showed that age (> 76 years), weight (≤ 58 kg), BMI (≤ 27.66 kg/m^2), WC (≤ 92 cm) and DCC (≤ 35 cm) were able to track confirmed sarcopenia. Tracking ability was not observed for education and height. In men, age (> 73 years), weight (≤ 71 kg), BMI (≤ 24.45 kg/m^2), WC (≤ 98 cm) and DCC (≤ 34 cm) were able to track confirmed sarcopenia. Education level and height were not able to track confirmed sarcopenia in men (**Table 3**).

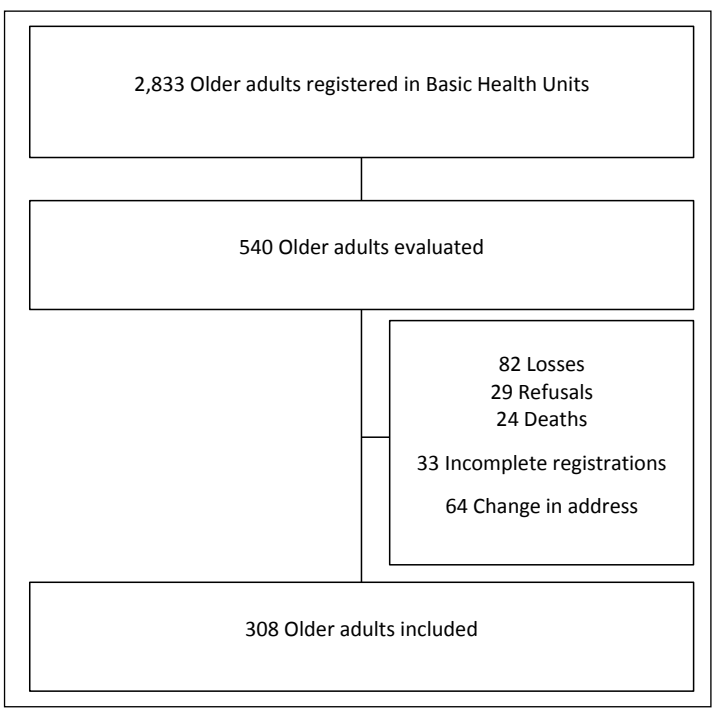


Figure 1. Flowchart depicting the sample selection process.

Table 1. Sociodemographic and anthropometric characteristics of the sample (n = 308)

Characteristic (mean ± SD)	Probable Sarcopenia		Confirmed Sarcopenia	
	No Sarcopenia	Sarcopenia	No Sarcopenia	Sarcopenia
Female (n, %)	78 (49.40%)	80 (50.60%)	151 (93.20%)	11 (6.80%)
Sociodemographic				
Age (years)	68.43 ± 6.10	69.8 ± 7.42	68.68 ± 6.18	78.18 ± 10.81*
Education (years)	6.05 ± 3.67	4.93 ± 3.73*	5.64 ± 3.78	3.72 ± 2.64
Anthropometric				
Body weight (kg)	69.11 ± 13.94	73.02 ± 14.98	73.58 ± 15.17	55.00 ± 4.28*
Height (m)	1.54 ± 0.06	1.55 ± 0.06	1.55 ± 0.06	1.54 ± 0.06
BMI (kg/m^2)	28.98 ± 5.67	30.04 ± 5.81	30.47 ± 5.98	23.29 ± 2.84*
WC (cm)	96.26 ± 11.79	100.51 ± 11.10*	99.88 ± 12.06	89.72 ± 6.23*
DCC (cm)	37.68 ± 4.17	37.74 ± 3.84	38.61 ± 5.13	33.18 ± 1.32*
Male (n, %)	74 (61.70%)	46 (38.30%)	113 (91.90%)	10 (8.10%)
Sociodemographic				
Age (years)	68.82 ± 6.67	71.45 ± 6. 55*	69.33 ± 6.59	74.30 ± 6.39*
Education (years)	6.28 ± 3.39	5.32 ± 3.91	6.01 ± 3.49	5.00 ± 4.89
Anthropometric				
Body weight (kg)	79.78 ± 17.07	78.63 ± 15.35	80.58 ± 16.14	64.90 ± 9.64*
Height (m)	168.52 ± 6.54	166.86 ± 7.21	167.57 ± 6.58	170.70 ± 8.65
BMI (kg/m^2)	28.02 ± 5.49	28.19 ± 5.04	28.63 ± 5.15	22.13 ± 1.69*
WC (cm)	102.37 ± 13.29	105.47 ± 14.15	104.69 ± 13.45	91.45 ± 8.26*
DCC (cm)	37.18 ± 4.00	36.83 ± 5.78	37.36 ± 4.77	33.39 ± 1.61*

*Differences between groups with and without sarcopenia (P < 0.05).
SD = standard deviation; BMI = body mass index; WC = waist circumference; DCC = dominant calf circumference.

Table 2. Accuracy of the anthropometric and sociodemographic variables for screening probable sarcopenia (n = 308)

Variable	Predictive value	AUC (CI 95%)	Sensitivity (CI 95%)	Specificity (CI 95%)	+LR (CI 95%)	–LR (CI 95%)
Female (n = 178)						
Sociodemographic						
Age (years)	--	0.54 (0.45; 0.63)	--	--	--	--
Education (years)	--	0.59 (0.50; 0.68)	--	--	--	--
Anthropometric						
Body weight (kg)	--	0.57 (0.48; 0.66)	--	--	--	--
Height (m)	--	0.55 (0.47; 0.64)	--	--	--	--
BMI (kg/m^2)	--	0.55 (0.46; 0.64)	--	--	--	--
WC (cm)	> 91	0.61 (0.53; 0.69)*	82.50% (72.4; 90.1)	42.31% (31.2; 54.0)	1.43 (1.2; 1.8)	0.41 (0.2; 0.7)
DCC (cm)	--	0.51 (0.42; 0.60)	--	--	--	--
Male (n = 130)						
Sociodemographic						
Age (years)	> 69	0.62 (0.52; 0.70)*	65.22% (49.8; 78.6)	60.27% (48.1; 71.5)	1.64 (1.2; 2.3)	0.58 (0.4; 0.9)
Education (years)	--	0.60 (0.49; 0.70)	--	--	--	--
Anthropometric						
Body weight (kg)	--	0.53 (0.42; 0.64)	--	--	--	--
Height (m)	--	0.56 (0.45; 0.67)	--	--	--	--
BMI (kg/m^2)	--	0.51 (0.40; 0.62)	--	--	--	--
WC (cm)	--	0.55 (0.44; 0.66)	--	--	--	--
DCC (cm)	--	0.50 (0.39; 0.61)	--	--	--	--

*P < 0.05; AUC = area under the ROC curve; ROC = receiver operating characteristic curve; +LR: odds ratio for positive test; –LR: odds ratio for negative test.
BMI = body mass index; WC = waist circumference; DCC = dominant calf circumference; CI = confidence interval.

In the adjusted multivariate logistic regression analysis, older women with WC > 91 cm had a 3.05 (95% CI: 1.40; 6.61) times greater chance of having probable sarcopenia than older women with WC < 91 cm. Older adults aged > 69 years were 2.56 (95% CI: 1.12; 5.82) times more likely to have probable sarcopenia than those aged < 69 years (**Table 4**).

Due to the low prevalence of sarcopenia confirmed in the sample, performing a multivariate logistic regression analysis for this condition was not possible.

DISCUSSION

The data from this study showed that WC > 91 cm in women and age > 69 years in men should be used in screening for probable sarcopenia. Age, weight, BMI, WC, and DCC were screening variables for both women and men for confirmed sarcopenia.

The prevalence of probable sarcopenia and confirmed sarcopenia in the present study was 50.60% and 6.80% in women and 38.30% and 8.10% in men, respectively. The prevalence of probable sarcopenia observed in this study was higher than that found by Wearing et al.[30] who reported it to be 26.3% for women and 28.0% for men in community-dwelling older Swiss adults. This difference in the reported prevalence of probable sarcopenia may be related to the sociodemographic, ethnic, and economic characteristics of the samples, as well as the measurement method, since probable sarcopenia was evaluated using 5XSST in this study, whereas in the study by Wearing et al.,[30] HGS was used.

Table 4. Results of multivariate logistic regression analysis between predictor variables and probable sarcopenia in community-dwelling older adults (n = 308)

Variables	Probable Sarcopenia	
	Unadjusted OR (CI 95%)	Adjusted[a] OR (CI 95%)
Female (178)		
WC > 91 cm		
No	1.00	1.00
Yes	3.41 (1.61; 7.24)	**3.05 (1.40; 6.61)***
Male (130)		
Age > 69 years		
No	1.00	1.00
Yes	2.55 (1.15; 5.59)	**2.56 (1.12; 5.82)***

[a]Adjusted for multimorbidity, depressive symptoms, level of leisure-time physical activity, and history of falls; *P < 0.05. WC = waist circumference; OR = odds ratio; CI = confidence interval.

Table 3. Accuracy of the anthropometric and sociodemographic variables for screening confirmed sarcopenia (n = 308)

Variable	Predictive value	AUC (CI 95%)	Sensitivity (CI 95%)	Specificity (CI 95%)	+LR (CI 95%)	−LR (CI 95%)
Female (n = 178)						
Sociodemographic						
Age (years)	> 76	0.75 (0.68; 0.82)*	72.73% (39.0; 94.0)	86.75% (80.3; 91.7)	5.49 (3.2; 9.5)	0.31 (0.1; 0.8)
Education (years)	--	0.64(0.49; 0.79)	--	--	--	--
Anthropometric						
Body weight (kg)	≤ 58	0.90 (0.85; 0.94)*	90.91% (58.7; 99.8)	87.42% (81.0; 92.3)	7.22 (4.6; 11.4)	0.10 (0.02; 0.7)
Height (m)	--	0.52 (0.35; 0.69)	--	--	--	--
BMI (kg/m^2)	≤ 27.66	0.88 (0.82; 0.93)*	100.00% (71.5; 100.0)	66.89% (58.8; 74.3)	3.02 (2.4; 3.8)	0.00
WC (cm)	≤ 92	0.76 (0.69; 0.83)*	81.82% (48.2; 97.7)	72.67% (64.8; 79.6)	2.99 (2.0; 4.4)	0.25 (0.07; 0.9)
DCC (cm)	≤ 35	0.88 (0.82; 0.93)*	100.00% (71.5; 100.0)	78.52% (71.1; 84.8)	4.66 (3.4; 6.3)	0.00
Male (n = 130)						
Sociodemographic						
Age (years)	> 73	0.71 (0.62; 0.79)*	60.00% (26.2; 87.8)	74.11% (65.0; 81.9)	2.32 (1.3; 4.2)	0.54 (0.3; 1.2)
Education (years)	--	0.62 (0.42; 0.82)	--	--	--	--
Anthropometric						
Body weight (kg)	≤ 71	0.81 (0.73; 0.88)*	90.00% (55.5; 99.7)	73.21% (64.0; 81.1)	3.36 (2.3; 4.9)	0.14 (0.02; 0.9)
Height (m)	--	0.66 (0.48; 0.83)	--	--	--	--
BMI (kg/m^2)	≤ 24.45	0.92 (0.85; 0.96)*	100.00% (69.2; 100.0)	83.93% (75.8; 90.2)	6.22 (4.1; 9.5)	0.00
WC (cm)	≤ 98	0.82 (0.74; 0.88)*	90.00% (55.5; 99.7)	72.97% (63.7; 81.0)	3.33 (2.3; 4.8)	0.14 (0.02; 0.9)
DCC (cm)	≤ 34	0.85 (0.77; 0.91)*	80.00% (44.4; 97.5)	85.71% (77.8;91.6)	5.60 (3.2; 9.7)	0.23 (0.07; 0.8)

*P < 0.05; AUC: Area under the ROC curve; ROC: receiver operating characteristic curve; +LR: odds ratio for positive test; −LR: odds ratio for negative test. BMI = body mass index; WC = waist circumference; DCC = and dominant calf circumference; CI = confidence interval.

Regarding the prevalence of confirmed sarcopenia, 6.80% of the women and 8.10% of the men had this condition. Similar findings were obtained by Esteves et al.[9] who observed a prevalence of 6.10% of confirmed sarcopenia in older Brazilian adults. Moreover, confirmation of sarcopenia was obtained with a reduction in muscle mass as assessed by Lee's equation[19] in the same manner as in the present study. These findings show the difference in prevalence when considering probable and confirmed sarcopenia, making it necessary to measure strength and muscle mass in older adults in clinical practice for early detection of the disease to reduce underreporting of sarcopenia in this population.

The present study suggests that an age > 69 years may be indicative of probable sarcopenia in men. Fragala et al.[18] observed that, in men, as muscle quality decreased, the time taken to perform 5XSST increased. Bai et al.[31] demonstrated that reduction in muscle strength directly affects the physical performance of older adults with aging. In addition, the literature shows that type II muscle fibers suffer neurodegeneration with aging, causing muscle tissue impairment, confirming the association between sarcopenia and age.[32] It is known that age is also related to confirmed sarcopenia, with higher prevalence in older age groups.[10,33] Data from the present study suggest that age > 73 years is a good determinant in screening for confirmed sarcopenia in men. Although age has shown significant results in screening probable and confirmed sarcopenia, no other study to date has suggested cutoff points for this variable.

Confirmed sarcopenia was screened in women aged > 76 years. This finding corroborates that of Albani et al.,[34] who observed a decrease in the concentration of growth factors similar to insulin type 1 in women aged 70 years. This growth factor is responsible for muscle growth and repair and is a triggering factor for the development of sarcopenia in older women.[33] Despite age being a nonmodifiable risk factor, the identification of cutoff points enables a warning sign for rehabilitation professionals, resulting in early diagnosis and intervention for the disease.

WC > 91 cm in women stands out as a possible anthropometric indicator for screening for probable sarcopenia. Evidence indicates that the accumulation of visceral fat in women may have a multifactorial cause, involving lifestyle, hormonal factors, body composition, reduced synthesis, and innervation of muscle proteins, in addition to impaired intramyocellular calcium metabolism.[18,35,36] In addition, the accumulation of visceral fat reduces muscle quality due to fat infiltration in the tissue, affecting muscle strength. Consequently, it can affect the functional capacity of older adults in aggravated circumstances, causing an excess of fat mass associated with a reduction in strength, termed sarcopenic obesity.[37] Kim et al.[38] observed that high WC (88.4 ± 9.1) was positively associated with functional limitation in older women, reinforcing the findings of this study. Furthermore, it appears that concomitant with the increase in WC, elevations in the levels of proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-6, and IL-1, are observed.[39] These act directly on skeletal muscle to facilitate muscle catabolism through pathways related to chronic inflammation and oxidative stress, thus contributing to the development of sarcopenia.[35,39]

Considering WC as a screening parameter for confirmed sarcopenia, cutoff points ≤ 92 and ≤ 98 cm are suggested for women and men, respectively. Baker et al.[40] observed that high adiponectin concentrations are associated with weight loss, low density, and skeletal muscle mass, in addition to functional limitation in older adults aged 70–79 years, which may be a factor for the development of sarcopenia in individuals of this age group.[41] Casals et al.[42] observed that the reduction of muscle mass in older adults can negatively affect glucose regulation, impacting muscle tissue. When comparing the results of this study with those of Esteves et al.[9] (WC: ≤ 86 cm for women and ≤ 97 cm for men) and Confortini et al.[11] (WC: 88 cm for women and 92 cm for men), the results were higher in sensitivity for both sexes and in specificity for men, reinforcing the utility of WC as a viable indicator for sarcopenia in clinical practice.

Weight and BMI proved to be effective variables for screening for confirmed sarcopenia in both sexes. The cutoff points for weight were ≤ 58 and ≤ 71 kg for women and men, respectively. For BMI, the suggested values were ≤ 27.66 kg/m² for women and ≤ 24.45 kg/m² for men. Beaudart et al.[8] observed a strong association between BMI and muscle mass reduction in older adults with sarcopenia. Although BMI is not only related to muscle mass, it is believed that lower values in older people with sarcopenia are due to disease. characteristics, such as reduced muscle mass.[9,11,12] Studies using BMI as a predictor for confirmed sarcopenia found results similar to those of this study, suggesting a cutoff point for women at ≤ 24.5 kg/m² (sensitivity: 100.00%; specificity: 81.78%) and for men at ≤ 24.8 kg/m² (sensitivity: 100%; specificity: 74.22%).[9] BMI cutoff values were also suggested by Confortin et al.[11] for women at 26.2 kg/m² (sensitivity: 74.60%; specificity: 85.70%) and for men at 24.6 kg/m² (sensitivity: 84.90%; specificity: 63.30%), confirming BMI as a good indicator for screening for sarcopenia.

Based on the data analyzed, DCC could also be used as an anthropometric variable to predict confirmed sarcopenia in both sexes. Studies using DCC to predict confirmed sarcopenia observed similar results to those found in the current study. For example, Barbosa-Silva et al.[10] suggested a cutoff point of ≤ 33 cm (sensitivity: 100.00%; specificity: 76.00%) for women and ≤ 34 cm (sensitivity: 61.00%; specificity: 76.00%) for men. Esteves et al.[9] also suggested DCC cutoff points of ≤ 31 cm (sensitivity: 93.33%; specificity: 67.05%) for women and ≤ 33 cm (sensitivity: 90.00%; specificity: 60.16%) for men. In addition, the study translating

SARC-F questionnaire into Portuguese (Brazilian) proposed that using the instrument, DCC should be measured in Brazilian older adult population with a cutoff point of ≤ 33 cm for women and ≤ 34 cm for men, with lower sensitivity and specificity than those found in this study.[43]

These findings suggest the utility of DCC in screening for confirmed sarcopenia.[9,11,12,43] DCC is a sensitive anthropometric measure for muscle mass in older adults.[44] This is a useful factor to detect the presence of confirmed sarcopenia when there is a reduction in muscle mass in this population. However, the use of DCC in older adults has limitations, such as the impossibility of separating muscle tissue from intramuscular or subcutaneous adipose tissue.[43] The use of DCC is unfeasible in the detection of probable sarcopenia, as its diagnosis will only be made when a reduction in muscle strength is observed.

Thus, as in the findings of this study, WC, DCC, and BMI are shown as good indicators in the literature in screening for sarcopenia in the older adult population in general.[9-11] However, the use of gold standard instruments is recommended to assess muscle mass in obese individuals, as the values will be far below the suggested cutoff points due to possible sarcopenic obesity characterized by dysregulated secretion of adipokines, proinflammatory cytokines, and decreased adiponectin, which cause expansion and dysfunction in the adipose tissue. This, in turn, induces catabolism, chronic inflammation, and increased secretion of proinflammatory myokines in the muscle tissue, causing muscle dysfunction and exacerbation of adipose tissue inflammation, thus establishing a vicious cycle triggering the pathogenic cascade of the disease.[39,43,45]

Despite the relevance of the findings, some limitations should be highlighted, such as the use of the Lee equation to measure muscle mass. Although the use of this equation demonstrates a high correlation rate in community-dwelling older adult population when compared with DXA, it is not considered the gold standard for muscle strength assessment. However, considering the practical applicability of these findings, these diagnostic tools are not easily available, in addition to exposing older adults to high levels of radiation. Furthermore, it is noteworthy that it was not possible to perform multivariate logistic regression analysis for the confirmed sarcopenia sample because of the small sample size for this category (n = 21).

On the other hand, the study's strong point is the recommendation of sociodemographic and anthropometric cutoff points that help in the screening for early stage sarcopenia and confirming the condition in community-dwelling older adults. In addition, it is highlighted that this screening can be carried out through low-cost, easy, and quick assessments, enabling health professionals to carry out early and effective interventions for the disease in clinical practice.

CONCLUSION

Sociodemographic and anthropometric variables are simple and accessible tools in screening for sarcopenia in older people. In this sense, our data suggest the use of waist circumference for women and age for men as variables capable of tracking probable sarcopenia in older adults.

REFERENCES

1. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31. Erratum in: Age Ageing. 2019;48(4):601. PMID: 30312372; https://doi.org/10.1093/ageing/afy169.
2. Shafiee G, Keshtkar A, Soltani A, et al. Prevalence of sarcopenia in the world: a systematic review and meta- analysis of general population studies. J Diabetes Metab Disord. 2017;16:21. PMID: 28523252; https://doi.org/10.1186/s40200-017-0302-x.
3. Diz JB, Leopoldino AA, Moreira BS, et al. Prevalence of sarcopenia in older Brazilians: A systematic review and meta-analysis. Geriatr Gerontol Int. 2017;17(1):5-16. PMID: 26799062; https://doi.org/10.1111/ggi.12720.
4. Veronese N, Demurtas J, Soysal P, et al. Sarcopenia and health-related outcomes: an umbrella review of observational studies. Eur Geriatr Med. 2019;10(6):853-62. PMID: 34652767; https://doi.org/10.1007/s41999-019-00233-w.
5. Abreu DROM, Novaes ES, Oliveira RR, Mathias TAF, Marcon SS. Fall-related admission and mortality in older adults in Brazil: trend analysis. Cien Saude Colet. 2018;23(4):1131-41. PMID: 29694573; https://doi.org/10.1590/1413-81232018234.09962016.
6. Marzetti E, Calvani R, Tosato M, et al. Sarcopenia: an overview. Aging Clin Exp Res. 2017;29(1):11-7. PMID: 28155183; https://doi.org/10.1007/s40520-016-0704-5.
7. Borges VS, Lima-Costa MFF, Andrade FB. A nationwide study on prevalence and factors associated with dynapenia in older adults: ELSI-Brazil. Cad Saude Publica. 2020;36(4):e00107319. PMID: 32374810; https://doi.org/10.1590/0102-311X00107319.
8. Beaudart C, McCloskey E, Bruyère O, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr. 2016;16(1):170. PMID: 27716195; https://doi.org/10.1186/s12877-016-0349-4.
9. Esteves CL, Ohara DG, Matos AP, et al. Anthropometric indicators as a discriminator of sarcopenia in community-dwelling older adults of the Amazon region: a cross-sectional study. BMC Geriatr. 2020;20(1):518. PMID: 33261567; https://doi.org/10.1186/s12877-020-01923-y.
10. Barbosa-Silva TG, Bielemann RM, Gonzalez MC, Menezes AM. Prevalence of sarcopenia among community-dwelling elderly of a medium-sized South American city: results of the COMO VAI? study. J Cachexia Sarcopenia Muscle. 2016;7(2):136-43. Erratum in: J Cachexia Sarcopenia Muscle. 2016;7(4):503. PMID: 27493867; https://doi.org/10.1002/jcsm.12049.
11. Confortin SC, Meneghini V, Ono LM, et al. Anthropometric indicators as a screening tool for sarcopenia in older adults from Florianópolis,

Santa Catarina: EpiFloripa Ageing study. Rev Nutri. 2017;30(3):287-96. https://doi.org/10.1590/1678-98652017000300002.

12. Pinheiro PA, Coqueiro RDS, Carneiro JAO, et al. Anthropometric indicators as screening tools for sarcopenia in older adult women. Enferm Clin (Engl Ed). 2020;30(4):269-74. PMID: 30737176; https://doi.org/10.1016/j.enfcli.2018.12.010.
13. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23. PMID: 20392703; https://doi.org/10.1093/ageing/afq034.
14. Levine DM, Berenson ML, Stephan D. Estatística: Teoria e Aplicações usando Microsoft Excel em Português. Rio de Janeiro: LTC; 2000.
15. Lohman TG, Roche AF, Martorel R. Anthropometric standardization reference manual. 1st ed. USA: Human Kinetics Books; 1988.
16. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253. PMID: 11234459.
17. Cesari M, Kritchevsky SB, Newman AB, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. J Am Geriatr Soc. 2009;57(2):251-9. PMID: 19207142; https://doi.org/10.1111/j.1532-5415.2008.02126.x.
18. Fragala MS, Clark MH, Walsh SJ, et al. Gender differences in anthropometric predictors of physical performance in older adults. Gend Med. 2012;9(6):445-56. PMID: 23123187; https://doi.org/10.1016/j.genm.2012.10.004.
19. Lee RC, Wang Z, Heo M, et al. Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. Am J Clin Nutr. 2000;72(3):796-803. Erratum in: Am J Clin Nutr. 2001;73(5):995. PMID: 10966902; https://doi.org/10.1093/ajcn/72.3.796.
20. Rech CR, Dellagrana RA, Marucci MFN, Petroski EL. Validade de equações antropométricas para estimar a massa muscular em idosos. Rev Bras Cineantropom Desemp Hum. 2012;14(1):23-31. https://doi.org/10.5007/1980-0037.2012v14n1p23.
21. Moreira VG, Perez M, Lourenço RA. Prevalence of sarcopenia and its associated factors: the impact of muscle mass, gait speed, and handgrip strength reference values on reported frequencies. Clinics (Sao Paulo). 2019;74:e477. PMID: 30994709; https://doi.org/10.6061/clinics/2019/e477.
22. World Health Organization. The world health report 2008: primary health care now more than ever. Geneva: World Health Organization; 2008. Available from: https://apps.who.int/iris/handle/10665/43949. Accessed in 2022 (Sep 16).
23. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry. 1999;14(10):858-65. PMID: 10521885; https://doi.org/10.1002/(sici)1099-1166(199910)14:10≤858::aid-gps35≥3.0.co;2-8.
24. 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. Rev Bras Cien Mov. 2004;12(1):25-34. https://doi.org/10.18511/rbcm.v12i1.538.
25. Benedetti TB, Antunes PC, Rodriguez-Añez CR, Mazo GZ, Petroski EL. Reprodutibilidade e validade do Questionário Internacional de Atividade Física (IPAQ) em homens idosos. Rev Bras Med Esporte. 2007;13(1). https://doi.org/10.1590/S1517-86922007000100004.
26. WHO Guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/336656/9789240015128-eng.pdf. Accessed in 2022 (Aug 30).
27. Lopes KT, Costa DF, Santos LF, Castro DP, Bastone AC. Prevalence of fear of falling among a population of older adults and its correlation with mobility, dynamic balance, risk and history of falls. Braz J Phys Ther. 2009;13(3):223-9. https://doi.org/10.1590/S1413-35552009005000026.
28. Pimentel RM, Scheicher ME. Comparação do risco de queda em idosos sedentários e ativos por meio da escala de equilíbrio de Berg. Fisioter Pesqui. 2009;16(1):6-10. https://doi.org/10.1590/S1809-29502009000100002.
29. Liu-Ambrose T, Davis JC, Best JR, et al. Effect of a home-based exercise program on subsequent falls among community-dwelling high-risk older adults after a fall: a randomized clinical trial. JAMA. 2019;321(21):2092-2100. Erratum in: JAMA. 2019;322(2):174. PMID: 31162569; https://doi.org/10.1001/jama.2019.5795.
30. Wearing J, Konings P, de Bie RA, Stokes M, de Bruin ED. Prevalence of probable sarcopenia in community-dwelling older Swiss people - a cross-sectional study. BMC Geriatr. 2020;20(1):307. PMID: 32847545; https://doi.org/10.1186/s12877-020-01718-1.
31. Bai HJ, Sun JQ, Chen M, et al. Age-related decline in skeletal muscle mass and function among elderly men and women in Shanghai, China: a cross sectional study. Asia Pac J Clin Nutr. 2016;25(2):326-32. PMID: 27222416; https://doi.org/10.6133/apjcn.2016.25.2.14.
32. Lang T, Streeper T, Cawthon P, et al. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int. 2010;21(4):543-59. PMID: 19779761; https://doi.org/10.1007/s00198-009-1059-y.
33. Yamada M, Nishiguchi S, Fukutani N, et al. Prevalence of Sarcopenia in Community-Dwelling Japanese Older Adults. J Am Med Dir Assoc. 2013;14(12):911-5. PMID: 24094646; https://doi.org/10.1016/j.jamda.2013.08.015.
34. Albani D, Batelli S, Polito L, et al. A polymorphic variant of the insulin-like growth factor 1 (IGF-1) receptor correlates with male longevity in the Italian population: A genetic study and evaluation of circulating IGF-1 from the "Treviso Longeva (TRELONG)" study. BMC Geriatr. 2009;9:19. PMID: 19460140; https://doi.org/10.1186/1471-2318-9-19.
35. Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcopenic Obesity: Epidemiologic Evidence, Pathophysiology, and Therapeutic Perspectives. Curr Obes Rep. 2019;8(4):458-71. PMID: 31654335; https://doi.org/10.1007/s13679-019-00359-9.

36. Petroni ML, Caletti MT, Dalle Grave R, et al. Prevention and Treatment of Sarcopenic Obesity in Women. Nutrients. 2019;11(6):1302. PMID: 31181771; https://doi.org/10.3390/nu11061302.
37. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018;14(9):513-37. PMID: 30065268; https://doi.org/10.1038/s41574-018-0062-9.
38. Kim JH, Choi SH, Lim S, et al. Sarcopenia and obesity: gender-different relationship with functional limitation in older persons. J Korean Med Sci. 2013;28(7):1041-7. Erratum in: J Korean Med Sci. 2013;28(9):1411. PMID: 23853487; https://doi.org/10.3346/jkms.2013.28.7.1041.
39. Sakuma K, Yamaguchi A. Sarcopenic obesity and endocrinal adaptation with age. Int J Endocrinol. 2013;2013:204164. PMID: 23690769; https://doi.org/10.1155/2013/204164.
40. Baker JF, Newman AB, Kanaya A, et al. The Adiponectin Paradox in the Elderly: Associations With Body Composition, Physical Functioning, and Mortality. J Gerontol A Biol Sci Med Sci. 2019;74(2):247-53. PMID: 29438496; https://doi.org/10.1093/gerona/gly017.
41. Sanz B, Arrieta H, Hervás G, et al. Serum adiponectin is associated with body composition and cognitive and psychological status in older adults living in long-term nursing homes. Exp Gerontol. 2019;121:1-9. PMID: 30885718; https://doi.org/10.1016/j.exger.2019.03.005.
42. Casals-Vázquez C, Suárez-Cadenas E, Estébanez Carvajal FM, et al. Relación entre calidad de vida, actividad física, alimentación y control glucémico con la sarcopenia de adultos mayores con diabetes mellitus tipo 2 [Relationship between quality of life, physical activity, nutrition, glycemic control and sarcopenia in older adults with type 2 diabetes mellitus]. Nutr Hosp. 2017;34(5):1198-204. PMID: 29130720; https://doi.org/10.20960/nh.1070.
43. Barbosa-Silva TG, Menezes AM, Bielemann RM, et al. Enhancing SARC-F: Improving Sarcopenia Screening in the Clinical Practice. J Am Med Dir Assoc. 2016;17(12):1136-41. PMID: 27650212; https://doi.org/10.1016/j.jamda.2016.08.004.
44. Ling CHY, Meskers CGM, Maier AB. Can anthropometric measures be used as proxies for body composition and physical function in geriatric outpatients? Arch Gerontol Geriatr. 2021;94:104379. PMID: 33610124; https://doi.org/10.1016/j.archger.2021.104379.
45. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev. 2017;35:200-21. PMID: 27702700; https://doi.org/10.1016/j.arr.2016.09.008.

Authors' contributions: de Souza L: formal analysis (equal), investigation (equal), methodology (equal), writing—original draft (equal) and writing—review and editing (equal); Fontanela LC: formal analysis (equal, writing-original draft (equal) and writing-review and editing (equal); Leopoldino AAO: formal analysis (equal), writing—original draft (equal) and writing-review and editing (equal); Mendonça VA: writing—review and editing (equal); Danielewicz AL: formal analysis (equal), investigation (equal), methodology (equal), writing—original draft (equal) and writing—review and editing (equal); Lacerda ACR: formal analysis (equal), investigation (equal), methodology (equal), writing—original draft (equal) and writing-review and editing (equal); and Avelar NCP: formal analysis (equal), investigation (equal), methodology (equal), writing—original draft (equal) and writing—review and editing (equal). All authors actively contributed to the discussion of the study results and all reviewed and approved the final version to be published

Acknowledgments: The authors are grateful to the Municipal Health Secretariat and the professionals who work in the Basic Health Units of the municipality Balneário Arroio do Silva of Santa Catarina for assisting in conducting the project and facilitating contact with the sampled older adult population

Sources of funding: This work was carried out with the support of Programa Institucional de Bolsas de Iniciação Científica/Conselho Nacional de Desenvolvimento Científico e Tecnológico (PIBIC/CNPq) (Edital Pró-Reitoria de Pesquisa [Propesq] 01/2020) associated to the Pro-Rectory of Research of the Universidade Federal de Santa Catarina (UFSC) and CNPq (402574/2021-4)
Conflicts of interest: None

Date of first submission: March 12, 2022
Last received: June 28, 2022
Accepted: August 17, 2022

Address for correspondence:
Núbia Carelli Pereira de Avelar
Universidade Federal de Santa Catarina (UFSC)
Rod. Governador Jorge Lacerda, 3.201
Jardim das Avenidas — Araranguá (SC) — Brasil
CEP 88040-900
Tel. (+55 48) 9988-8489
E-mail: nubia.carelli@ufsc.br

Prevalence risk of sarcopenia in older Brazilian adults during the pandemic: A cross-sectional analysis of the Remobilize Study

Patricia Parreira Batista[I], Monica Rodrigues Perracini[II], Juleimar Soares Coelho de Amorim[III], Maria do Carmo Correia de Lima[IV], Camila Astolphi Lima[V], Daniele Sirineu Pereira[VI], Renata Gonçalves Dantas[VII], Etiene Oliveira da Silva Fittipaldi[VIII], Aurélio Dias Santos[IX], Hércules Lázaro Morais Campos[X], Leani Souza Máximo Pereira[XI]

Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil

[I]PT, MSc. Doctoral Student Postgraduate Program in Rehabilitation Sciences, Department of Physiotherapy, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil. https://orcid.org/0000-0002-8036-882X

[II]PT, PhD. Professor, Master's and Doctoral Programs in Physical Therapy, Universidade Cidade de São Paulo (UNICID), São Paulo (SP), Brazil; Master's and Doctoral Programs in Gerontology, Faculty of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil. https://orcid.org/0000-0001-9331-3820

[III]PT, PhD. Professor, Physical Therapy Course, Instituto Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brazil. https://orcid.org/0000-0003-3218-1769

[IV]PT, PhD. Faculty of Medical Sciences, Master's and Doctoral Programs in Gerontology, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil. https://orcid.org/0000-0001-9018-5325

[V]PT, PhD. Postdoctoral Student of Master's and Doctoral Program in Physical Therapy, Universidade Cidade de São Paulo (UNICID), São Paulo (SP), Brazil. https://orcid.org/0000-0001-9882-6975

[VI]PT, PhD. Professor, Postgraduate Program in Rehabilitation Sciences, Department of Physiotherapy, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil. https://orcid.org/0000-0002-4868-9244

[VII]PT, MSc. Doctoral Student of Master's and Doctoral Program in Physical Therapy, Universidade Cidade de São Paulo (UNICID), São Paulo (SP), Brazil; and Professor of Physical Therapy, Universidade Estadual do Sudoeste da Bahia (UESB), Vitória da Conquista (BA), Brazil. https://orcid.org/0000-0002-1575-7204

[VIII]PT, PhD. Professor, Department of Physiotherapy, Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil. http://orcid.org/0000-0002-1524-6930

[IX]PT, MSc. Professor, Department of Physiotherapy, Centro Universitário Dr. Leão Sampaio (UNILEÃO), Juazeiro do Norte (CE), Brazil. https://orcid.org/0000-0003-3693-9864

[X]PT, MSc. Professor, Department of Physiotherapy, Universidade Federal do Amazonas/Instituto de Saúde e Biotecnologia (UFAM/ISB), Coari (AM), Brazil. Doctoral Student, Postgraduate Program in Public Health, Universidade Federal do Espírito Santo (UFES), Vitória (ES), Brazil. https://orcid.org/0000-0002-6919-8161

[XI]PT, PhD. Professor, Postgraduate Program in Rehabilitation Sciences, Department of Physiotherapy, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil. https://orcid.org/0000-0001-7253-4392

KEY WORDS (MeSH terms):
Sarcopenia.
Mobility limitation.
Aged.
Physical distancing.
Pandemics.

AUTHORS' KEY WORDS:
SARC-F.
Risk of sarcopenia.
Screening.
Older adults.

ABSTRACT

BACKGROUND: Social distancing has led to lifestyle changes among older adults during the coronavirus disease 2019 (COVID-19) pandemic.

OBJECTIVES: This study aimed to estimate the prevalence risk of sarcopenia (RS) and investigate its associated factors during the COVID-19 pandemic in older Brazilian adults.

DESIGN AND SETTING: Cross-sectional observational analysis of baseline data as part of the Remobilize Study.

METHODS: Participants in the study were older adults (≥ 60 years), excluding those who were bedridden or institutionalized. The data collected consisted of answers about the RS (SARC-F), functional status, walking, sedentary behavior (SB), pain, comorbidity, and life space mobility.

RESULTS: A total of 1,482 older adults (70 ± 8.14 years, 74% women) participated in the study, and an RS prevalence of 17.1% was found. (95% confidence interval [CI] 15.25–19.15%). The adjusted multivariate model showed a significant association between RS and functional limitation (odds ratio [OR]: 19.05; CI 13.00–28.32), comorbidity (OR: 5.11; CI 3.44–7.81), pain (OR: 4.56; CI 3.33–6.28), total walking (OR: 0.99; CI 0.99–1.00), SB of 8–10 hours (OR: 1.85; CI 1.15–2.93), and SB of > 10 hours (OR: 3.93; CI 2.48–6.22). RS was associated with mobility during the pandemic (OR: 0.97; CI 0.96–0.98). $P < 0.05$.

CONCLUSIONS: During the pandemic, the prevalence of RS in older Brazilians was estimated at 17.1%. Moderate to severe functional limitation, comorbidities, presence of pain, walking, longer SB period, and reduced life space mobility significantly contributed to RS in older adults during the pandemic.

INTRODUCTION

Social restriction policies and lifestyle changes favor a reduction in mobility and the level of physical activity (PA), leading to a higher proportion of inactive people and an increase in sedentary behaviors (SB) during the pandemic.[1-4] A decline in life space mobility contributes to a reduction in intrinsic capacity, higher risk of sarcopenia (RS), and other adverse health consequences.[5,6] After 7 days of total bed rest, there is already a significant deterioration in muscle function in community-dwelling older adults, and 2,000 steps per day are not enough to prevent these deleterious effects on the musculature.[7] Coker et al. reported that a 15-day bed rest induces a significant reduction in fat-free muscle mass, poor performance, and increased fat in older individuals, which negatively impacts their mobility.[8]

A longer SB time observed during the pandemic is related to a worse prognosis in health conditions and a higher RS.[1-3,7,9] These factors can alter the homeostasis between the pro- and anti-inflammatory systemic components and muscle anabolism and catabolism, leading to the reduction of physiological reserves in older adults. Consequences such as increased plasma pro-inflammatory cytokines, greater muscle catabolism drive, and anabolic and insulin resistance lead to a deleterious cycle of muscle function, explaining the higher incidence of RS in this population.[1-3]

Sarcopenia is a generalized and progressive musculoskeletal disorder that is defined as a reduction in muscle mass and strength. It is a multifactorial disease with dynamic interrelationships and is commonly associated with a cascade of negative repercussions on health, functional limitation, and mortality.[10-12] Consequently, due to its considerable clinical impact on older individuals,

it increases health-related expenses and imposes a burden on the public health system, being more costly in socially unequal and/or developing countries, such as Brazil.[10,12,13] Updates from the European Working Group on Sarcopenia in Older People (EWGSOP2) and the Asian Working Group for Sarcopenia proposed the practice of population screening for RS in older people through strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire, a self-reported screening questionnaire.[10,14] Identifying sarcopenia in its early stages enables the control of its progression and/or reversal of the individual's clinical condition, thereby reducing the negative impacts caused by the disease.[3,10,11,14,15]

OBJECTIVE

Due to the abovementioned reasons, this study aimed to verify the prevalence of RS and investigate the factors associated with the presence of RS during the coronavirus disease 2019 (COVID-19) pandemic.

METHODS

Design and sample

This study presents a cross-sectional analysis of baseline data collected from May to July 2020 through an online questionnaire as part of the Remobilize Study (www.remobilize.com.br).[4] Using convenience snowball sampling, the online questionnaire (SurveyMonkey platform) was distributed throughout the Brazilian territory via social media (Facebook and Instagram), WhatsApp groups, social groups for older adults, and/or their friends and acquaintances. A pilot project for calibration and adjustments was conducted in advance. This study was approved by the University City of São Paulo Research Ethics Committee (May 18, 2020; CAAE 31592220.6.0000.0064) and is currently under progress.

The sample population consisted of community-dwelling older Brazilians (≥ 60 years) without distinction of sex, race, and/or social class. Following the exclusion criteria, those residing in long-term care facilities and/or bedridden were not eligible to participate in the study.[4] Participants who presented with disabilities were allowed to have the questions be answered by a family member or caregiver.[16] Participants without familiarity with the Internet were able to answer the survey via telephone.[4]

Measures

The sociodemographic, clinical, and lifestyle data are presented in **Table 1**. The self-reported functional comorbidity index questionnaire was used to detect the presence of comorbidities (two or more chronic diseases).[17] All participants answered questions about the presence or absence of pain.

The SARC-F questionnaire is recommended by the EWGSOP2 and the Asian Working Group for Sarcopenia as a population screening tool for RS.[10,14] The final score ranges from zero to ten points, and a score of ≥ 4 points identifies individuals with sarcopenia. SARC-F has a high specificity, but low to moderate sensitivity.[10,14,15,18] Population screening for RS (SARC-F) allows the exclusion of older patients with preserved muscle function in primary health care and identification of changes in the early stages of muscle function, functionality, and RS in older adults.[10,14,15,19]

Functional performance was assessed using the Older American Resources and Services questionnaire that has been translated and validated for the Brazilian population (BOMFAQ).[20,21] It is a self-report questionnaire on the ability to perform 15 functional activities (eight basic and seven instrumental tasks). The scores for the activities performed with difficulty or requiring help were added, ranging from 0–15 points. Older adults were classified based on their scores: no (0), slight (1–3), moderate (4–6), and severe (> 7) functional limitation.[22]

SB was assessed using one question about the duration of sitting activities in the prior week, referring to indoor activities (≤ 4 hours/day, 5–7 hours/day, 8–10 hours/day or ≥ 10 hours/day). Walking, including PA, utilitarian walking, and walking time, was assessed using the Incidental and Planned Exercise Questionnaire.[23] Validated for older adults, this is a simple, self-report questionnaire probing on walking activities during the prior week, specifically on the frequency and duration of the activity. The final score for walking as physical exercise and utilitarian walking was given by the product of frequency and duration for each item (minutes/week). The total walking time was calculated as the sum of walking as PA and utilitarian walking.

Life space mobility was measured using the Life-Space Assessment (LSA).[24] It estimates the individual perspective of mobility relative to the spatial area in five levels of life space in the prior week: mobility in the rooms at home, outside the bedroom (level 1), outside the home (level 2), a neighborhood close to home (level 3), circulation within the municipality where they reside (level 4), and inter-municipal areas (level 5). The answers were based on the frequency and need for mobility devices. The score was calculated as the product of frequency and performance skill, extracting a score based on level and the total by the sum of levels (0–120 points). Higher final scores indicated better mobility performance in the life space.

Statistical analysis

The prevalence of RS in participants was estimated using a 95% confidence interval (CI). Descriptive statistics were performed using absolute and relative frequencies for the total sample and RS, respectively. Continuous variables did not show a normal distribution in the Shapiro–Wilk test; therefore, the data are presented as medians and interquartile ranges. To compare the

Table 1. Total sample descriptive data and comparison between the groups with (strength, assistance with walking, rising from a chair, climbing stairs, and falls, SARC-F ≥ 4 points) and without risk of sarcopenia (RS) (SARC-F < 4 points)

		SARC-F		P value
		< 4 points (n = 1,228)	≥ 4 points (n = 254)	
Age, %	60–69 years	61.3%	31.5%	< 0.0001
	70–79 years	28.8%	26.0%	
	80 years and older	9.9%	42.5%	
Sex, %	Male	27.9%	16.9%	0.001
	Female	72.1%	83.1%	
Marital status, %	Single	10.3%	10.2%	< 0.0001
	Married	56.7%	39.0%	
	Divorced	12.7%	11.0%	
	Widowed	20.3%	39.8%	
Education, %	Illiterate	6.4%	14.9%	< 0.0001
	1–4 years	16.5%	31.5%	
	5–8 years	11.9%	13.8%	
	9 years or more	65.2%	39.8%	
Income[a], %	Up to 1× minimum wage	32.6%	44.1%	< 0.0001
	2–3× minimum wage	27.9%	27.9%	
	4–7× minimum wage	19.4%	11%	
	8–10× minimum wage	7.6%	7.9%	
	More than 10× minimum wage	12.5%	9.1%	
Occupation, %	Active	39.2%	24.8%	< 0.0001
	Inactive	55.3%	61.8%	
	Unemployed	5.5%	13.4%	
Sitting time, %	< 4 hours	48.6%	28.8%	< 0.0001
	5–7 hour	31.0%	31.1%	
	8–10 hour	12.6%	16.9%	
	> 10 hours	7.8%	23.2%	
BOMFAQ (4 pts +), %		10.3%	73.6%	< 0.0001
Comorbidities (≥ 2), %		50.40%	87.40%	< 0.0001
Pain (yes), %		21.6%	55.5%	< 0.0001
Walking (exercise) Med (IQR)		0 (0–25.31)	0 (0–0)	< 0.0001
Walking (utilitarian) Med (IQR)		7.5 (0–33.75)	0 (0; 0)	< 0.0001
Walking (total) Med (IQR)		7.5 (0; 101.20)	0 (0; 7.5)	< 0.0001
LSA - During pandemic Med (IQR)	Total score	36 (24; 52)	24 (12; 32)	< 0.0001
	Level 1	8 (8; 8)	8 (6; 8)	< 0.0001
	Level 2	16 (12; 16)	12 (4; 16)	< 0.0001
	Level 3	6 (0; 12)	0 (0; 6)	< 0.0001
	Level 4	8 (0; 16)	0 (0; 4)	< 0.0001
	Level 5	0 (0; 0)	0 (0; 0)	0.0002

Med = median; IQR = interquartile range (1st and 3rd IQR); LSA = Life-Space Assessment; BOMFAQ = Brazilian OARS Multidimensional Functional Assessment Questionnaire; a score of four points or more refers to the presence of moderate to severe functional limitation; walking (as exercise, utilitarian, and total) in the previous week (min/week). [a]minimum wage in Brazil = R$ 1,100.00 per month, corresponding to US$ 194.01 (April 5, 2021).

groups with and without RS, Pearson's chi-square test was used for categorical variables and the Mann–Whitney test was used for continuous variables. The association between independent variables and outcome was based on odds ratios (ORs) estimates and their respective CIs through logistic regression without (crude model) and with adjustment (adjusted model). All analyses were performed using Stata 14.0 (StataCorp LLC, College Station, Texas, United States), with a 5% statistical significance level.

RESULTS

A total of 1,482 participants were included in this study, and the study flowchart is shown in **Figure 1**. The prevalence of RS

during the pandemic was 17.1% (CI 15.25–19.15%). The distribution of SARC-F and total score items by age group and total scores are shown in **Figure 2**. Statistically significant differences were observed between the groups with and without RS in terms of age, sex, marital status, education, income, occupation, walking (exercise, utilitarian, and total), sitting time, functional limitation, presence of comorbidities, and pain. The RS group had a higher proportion of participants aged 80 years or older (42.5%), women (83.1%), lower income (44.1%), and 73.6% presented with moderate to severe functional limitation (**Table 1**). There were statistically significant differences in total LSA scores during the pandemic. Lower LSA scores were observed in older patients with RS. During the pandemic, there was a difference between older patients with and without RS for all walking variables (exercise and total), with lower values in the RS group.

Crude logistic regression analysis showed a significant association for all analyzed variables. After adjusting for sociodemographic factors, the following variables remained statistically significant, as seen in **Table 2**: moderate to severe functional limitations, comorbidity, pain, walking (exercise and total), SB 8–10 hours, SB > 10 hours, and total LSA score during the pandemic.

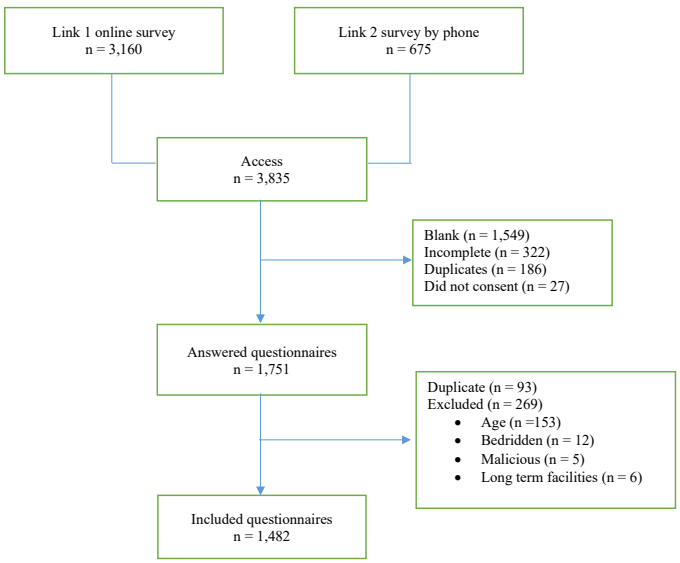


Figure 1. Study flowchart.

DISCUSSION

The results showed a high prevalence of RS in older Brazilians at the beginning of the COVID-19 pandemic in Brazil and a substantial association between RS and moderate to severe functional limitation, comorbidities, pain, and a positive gradient with the number of hours in SB. The OR for RS increased from 1.85 in older patients who reported 8 to 10 hours of SB to 3.93 in those with 10 hours or more of SB. Older patients with moderate to severe functional limitation were 19.05 times more likely to be at RS. Furthermore, greater mobility in living spaces lowered the chances of RS during the pandemic.

The prevalence of RS (17.1%) in the present study was substantially higher than that found in studies before the COVID-19 pandemic.[25-28] Dodds et al. reported a 4% prevalence of RS in 1,686 British older adults (aged ≥ 69 years),[25] while Kim and Won reported a rate of 7.5% among 2,123 Korean older adults (75.9 years).[26] Studies with a model of activity reduction (steps per day) in elders pointed to negative repercussions of greater catabolic drive on their musculature and metabolic and inflammatory markers during a short period of mobility restriction.[29,30] With a

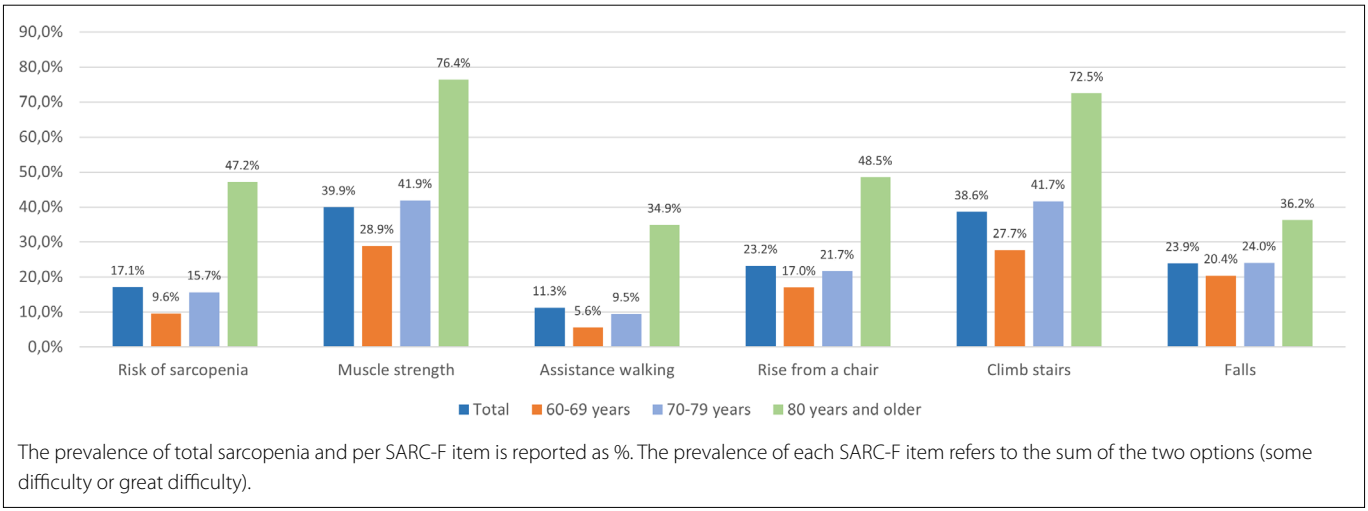


Figure 2. Prevalence of risk of sarcopenia in the total sample and by age group. Frequency of the items included in the strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire for older at risk for sarcopenia.

Table 2. Logistic regression analysis to verify the association of the factors contributing to the risk of sarcopenia

		Crude model			Adjusted model		
		OR	95% CI	P value	OR	95% CI	P value
BOMFAQ (4 pts +) (ref.: 0–3 pts)		24.20	17.42; 33.40	< 0.001	19.05	13.00; 28.32	< 0.001
Comorbidities (≤ 2) (ref.: 0–1)		6.82	4.70; 10.22	< 0.001	5.11	3.44; 7.81	< 0.001
Pain (ref.: absence of)		4.54	3.42; 6.03	< 0.001	4.56	3.33; 6.28	< 0.001
Walking (exercise)		0.99	0.986; 0.994	< 0.001	0.99	0.989; 0.997	0.001
Walking (utilitarian)		0.99	0.994; 0.999	0.041	0.99	0.997; 1.001	0.346
Walking (total)		0.99	0.993; 0.997	< 0.001	0.99	0.995; 0.999	0.008
Sedentary behavior (sitting time; ref. < 4 hours)	5–7 hour	1.69	1.20; 2.39	0.003	1.41	0.97; 2.04	0.072
	8–10 hour	2.26	1.48; 3.42	< 0.001	1.85	1.15; 2.93	0.01
	> 10 hours	5.02	3.34; 7.53	< 0.001	3.93	2.48; 6.22	< 0.001
LSA - During pandemic	Total score	0.95	0.94; 0.96	< 0.001	0.97	0.96; 0.98	< 0.001
	Level 1	0.79	0.74; 0.84	< 0.001	0.83	0.77; 0.89	< 0.001
	Level 2	0.90	0.88; 0.92	< 0.001	0.92	0.90; 0.95	< 0.001
	Level 3	0.92	0.91; 0.94	< 0.001	0.95	0.93; 0.97	< 0.001
	Level 4	0.93	0.91; 0.95	< 0.001	0.97	0.95; 0.98	< 0.001
	Level 5	0.92	0.88; 0.96	< 0.001	0.96	0.91; 0.99	0.047

Med = median; IQT= interquartile range (1st and 3rd IQR); LSA = Life-Space Assessment; BOMFAQ = Brazilian OARS Multidimensional Functional Assessment Questionnaire; a score of four points or more refers to the presence of moderate to severe functional limitation. Walking (as exercise, utilitarian, and total) in the previous week (minutes/week).

76% reduction in steps per day (< 1,500 steps/day) in 14 days, Breen et al. demonstrated a 3.9% reduction in fat-free lean mass; reduced insulin sensitivity (43%); and increased pro-inflammatory cytokines, TNF-α (12%), and C-reactive protein (25%) levels in 10 healthy older adults after the intervention (72.3 years).[30] These findings may support the higher RS prevalence in our study.

In Brazil, Barbosa-Silva et al. reported that sarcopenia had a prevalence of 8.4% (EWGSOP1) in 179 older adults.[18] Sarcopenia (SARC-F ≥ 6 points) and muscle function decline (SARC-F ≥ 4 points) were 17.3% and 34.6%, respectively. The authors proposed the addition of calf circumference measurements to SARC-F to improve the instrument's measurement accuracy.[18] The EWGSOP2 establishes an overlap of muscle strength in relation to muscle mass as a primary parameter in the diagnosis of sarcopenia, as muscle strength is the most reliable measure of muscle function.[10] Furthermore, it is associated with adverse health outcomes and facilitates the use of the diagnostic algorithm in clinical practice.[10,15,31] Thus, the present study considered values ≥ 4 in the SARC-F as the cutoff point because of the improved accuracy in diagnosing muscle function in older Brazilian people and support from the scientific community.[10,14,15,17] In addition, it is impossible to conduct anthropometric measurements due to pandemic-related restrictions.

Findings on sociodemographic differences between participants with and without RS were similar to those found in studies before the pandemic, whether in older patients with RS or with sarcopenia or on diagnostic parameters for sarcopenia.[18,25-27,31-35] The difference in the presence of moderate to severe functional limitation between the groups was significant. After adjusted logistic regression, those with moderate to severe functional limitation were 19.05 times more likely to be at RS. Similar findings were reported by Rolland et al, with a sample of 3,025 French older adults (80.5 years).[33] The authors found a lower functional performance in older adults at RS compared to the total sample and a significant association with reduced functional performance based on the gait speed and chair stand test results (OR: -0.04; CI 0.05–0.03 and OR: 13.1; CI 11.5–14.7). Longitudinal analyses with a 6-year follow-up confirmed the ability of SARC-F score ≥ 4 points (RS) to predict reduced functional performance.[31]

Our logistic regression analysis, adjusted for sociodemographic factors, showed a significant association of the presence of comorbidity with RS, corroborating previous studies.[25,33] Given the context of the pandemic, the combination of psychobehavioral factors, such as stress, worse sleep quality, food routine, and mood, as well as medical treatment and functional rehabilitation discontinuation, increased physical inactivity and SB, which triggered an accelerated progression of established chronic diseases due to the greater active systemic pro-inflammatory profile and higher muscle catabolism drive. Thus, monitoring these factors in older adults is necessary during and after the pandemic, including sociodemographic factors and their specifications.[1,2,3,36]

Pain contributed to the highest RS among the participants in this study. Corroborating this study, Lustosa et al. investigated RS in 322 older Brazilian women complaining of non-specific acute

lower back pain, and the results showed an association between pain intensity and poor mobility and balance.[37] The authors pointed out that RS, if present in older women with lower back pain, can negatively influence functionality.[37] Pain is multifactorial and subjective. Moreover, psychosocial factors are known to interfere with pain and its pro-inflammatory process, and social isolation predisposes to the development of chronic pain.[38] Thus, pain in older people should not be neglected during and after the pandemic, and directions for non-pharmacological and pharmacological interventions should be considered.

A positive and significant association was observed between SB and RS, with a "dose-response" effect for a more extended period of SB, causing older adults with 10 h or more of SB per day to be 3.93 (CI 2.48–6.22; compared to < 4 hours) times more likely to be at RS. With a sample of 1,068 older adults (72.1 years), Tzeng et al. demonstrated that sitting for 7 hours or more per day was significantly associated with RS (OR: 1.98; CI 1.09–3.59).[39] Smith et al. also investigated the relationship between SB and sarcopenia in 14,585 older adults from six low- and middle-income countries.[40] The authors identified that regardless of the PA level and presence of comorbidities, 11 hours or more of SB increases RS by 2.14 times (CI 1.06–4.33; compared to < 4 hours), and each additional hour per day of SB was related to an increased risk of RS by 1.06 (CI 1.04–1.10).[40] Thus, our results confirm that the more sedentary the lifestyle during the pandemic, the greater the probability of RS and possibly the worse is the health condition and muscle function prognosis.

It is known that physical inactivity and PA levels below the recommendations proposed by the World Health Organization (WHO) are more frequent in older adults,[3,41,42] and sarcopenic individuals have lower PA levels than non-sarcopenic individuals.[25,34,43] In the present study, there was a difference in walking (exercise, utilitarian, and total) between the two groups, reflecting the low PA level in participants with RS during the pandemic. Saraiva et al. found a reduction in the practice of regular PA (≥ 3 times/week) during the pandemic in 557 older Brazilian (80 ± 8 years), ranging from 42% active (pre-pandemic) to 26% (during the pandemic).[44] Tzeng et al. showed that insufficiently active older adults had a 5.14 (CI 3.04–8.70) times higher RS.[39] Thus, physical inactivity is a modifiable risk factor for sarcopenia, and physical exercise is the first-line treatment for this muscle disease.[2,15,32]

Our results showed lower life space mobility during the pandemic in the RS group. A similar and significant difference was found in a study published before the pandemic.[45] In this study, the group without RS had lower average age, was more active, and presented with a lower percentage of comorbidity than the group with RS. Higher mobility rates are associated with better muscle function, functional and cognitive performance, and social support.[46] This finding serves as a warning for this target population, given the prolonged course of the pandemic and the deleterious relationship between restriction of outdoor mobility and skeletal musculature.

Some limitations of this study must be considered. Snowball sampling was carried out on an online platform, differentiating our sample from the general community. The participants could have had access to the Internet and a higher level of education or social support as opposed to the older Brazilian population in general. Our findings were extrapolated to older adults with characteristics similar to those of our sample. In addition, the study had a cross-sectional design, making it impossible to identify causality in the analyzed relationships. However, this cross-sectional analysis aimed to identify and verify RS and its contributing factors in the Rede Remobilize (Wave 1) cohort and establish a baseline for future longitudinal studies on the impacts of the pandemic and RS in older individuals. To our knowledge, this is the first study to assess RS in a consistent sample of community-dwelling older adults in Brazil during the pandemic. Finally, this study encourages the use of SARC-F in monitoring older patients because it is a viable tool in clinical practice for screening for muscle function decline and RS, as it allows for the adequacy of future health care actions in favor of healthy aging.[19,47]

CONCLUSIONS

Moderate to severe functional limitation, comorbidity, pain, longer period of SB, and reduced life space mobility significantly contributed to the RS in older Brazilian adults during the pandemic. Longitudinal studies monitoring functional trajectories and adverse health outcomes in older patients with RS during the pandemic should be encouraged to understand the associated modifiable factors and preventive actions against this critical muscle dysfunction.

REFERENCES

1. Moro T, Paoli A. When COVID-19 affects muscle: effects of quarantine in older adults. Eur J Transl Myol. 2020;30(2):9069. PMID: 32782767; https://doi.org/10.4081/ejtm.2019.9069.
2. Kirwan R, McCullough D, Butler T, et al. Sarcopenia during COVID-19 lockdown restrictions: long-term health effects of short-term muscle loss. Geroscience. 2020;42(6):1547-78. PMID: 33001410; https://doi.org/10.1007/s11357-020-00272-3.
3. Roschel H, Artioli GG, Gualano B. Risk of Increased Physical Inactivity During COVID-19 Outbreak in Older People: A Call for Actions. J Am Geriatr Soc. 2020;68(6):1126-8. PMID: 32392620; https://doi.org/10.1111/jgs.16550.
4. Perracini MR, de Amorim JSC, Lima CA, et al. Impact of COVID-19 Pandemic on Life-Space Mobility of Older Adults Living in Brazil: REMOBILIZE Study. Front Public Health. 2021;9:643640. PMID: 33898378; https://doi.org/10.3389/fpubh.2021.643640.

5. Webber SC, Porter MM, Menec VH. Mobility in older adults: a comprehensive framework. Gerontologist. 2010;50(4):443-50. PMID: 20145017; https://doi.org/10.1093/geront/gnq013.
6. Miyashita T, Tadaka E, Arimoto A. Cross-sectional study of individual and environmental factors associated with life-space mobility among community-dwelling independent older people. Environ Health Prev Med. 2021;26(1):9. PMID: 33461488; https://doi.org/10.1186/s12199-021-00936-2.
7. Arentson-Lantz E, Galvan E, Wacher A, Fry CS, Paddon-Jones D. 2,000 Steps/Day Does Not Fully Protect Skeletal Muscle Health in Older Adults During Bed Rest. J Aging Phys Act. 2019;27(2):191-7. PMID: 29989486; https://doi.org/10.1123/japa.2018-0093.
8. Coker RH, Hays NP, Williams RH, Wolfe RR, Evans WJ. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. J Gerontol A Biol Sci Med Sci. 2015;70(1):91-6. PMID: 25122628; https://doi.org/10.1093/gerona/glu123.
9. Gianoudis J, Bailey CA, Daly RM. Associations between sedentary behaviour and body composition, muscle function and sarcopenia in community-dwelling older adults. Osteoporos Int. 2015;26(2):571-9. PMID: 25245026; https://doi.org/10.1007/s00198-014-2895-y.
10. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601. Erratum for: Age Ageing. 2019;48(1):16-31. PMID: 31081853; https://doi.org/doi:10.1093/ageing/afy169.
11. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23. PMID: 20392703; https://doi.org/10.1093/ageing/afq034.
12. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health Outcomes of Sarcopenia: A Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169548. PMID: 28095426; https://doi.org/10.1371/journal.pone.0169548.
13. Bruyère O, Beaudart C, Ethgen O, Reginster JY, Locquet M. The health economics burden of sarcopenia: a systematic review. Maturitas. 2019;119:61-9. PMID: 30502752; https://doi.org/10.1016/j.maturitas.2018.11.003.
14. Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020;21(3):300-307.e2. PMID: 32033882; https://doi.org/10.1016/j.jamda.2019.12.012.
15. Dent E, Morley JE, Cruz-Jentoft AJ, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. J Nutr Health Aging. 2018;22(10):1148-61. PMID: 30498820; https://doi.org/10.1007/s12603-018-1139-9.
16. Maurus J, Terzer T, Benner A, et al. Validation of a proxy-reported SARC-F questionnaire for current and retrospective screening of sarcopenia-related functional impairments. J Cachexia Sarcopenia Muscle. 2022;13(1):264-75. PMID: 34898035; https://doi.org/10.1002/jcsm.12871.
17. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol. 2005;58(6):595-602. PMID: 15878473; https://doi.org/10.1016/j.jclinepi.2004.10.018.
18. Barbosa-Silva TG, Menezes AM, Bielemann RM, et al. Enhancing SARC-F: Improving Sarcopenia Screening in the Clinical Practice. J Am Med Dir Assoc. 2016;17(12):1136-41. PMID: 27650212; https://doi.org/10.1016/j.jamda.2016.08.004.
19. Cesari M, Marzetti E, Calvani R. Sarcopenia and SARC-F: "Perfect is the Enemy of Good". J Am Med Dir Assoc. 2021;22(9):1862-3. PMID: 34456011; https://doi.org/10.1016/j.jamda.2021.07.030.
20. Duke University Center for the Study of Aging and Human Development. Multi-dimensional Functional Assessment: The OARS methodology. Durham, NC: Duke University Center for the Study of Aging and Human Development; 1978.
21. Ramos LR, Toniolo J, Cendoroglo MS, et al. Two-year follow-up study of elderly residents in S. Paulo, Brazil: methodology and preliminary results. Rev Saude Publica. 1998;32(5):397-407. PMID: 10030055; https://doi.org/10.1590/s0034-89101998000500001.
22. Ferreira MT, Matsudo SM, Ribeiro MC, Ramos LR. Health-related factors correlate with behavior trends in physical activity level in old age: longitudinal results from a population in São Paulo, Brazil. BMC Public Health. 2010;10:690. PMID: 21067591; https://doi.org/10.1186/1471-2458-10-690.
23. Delbaere K, Hauer K, Lord SR. Evaluation of the incidental and planned activity questionnaire (IPEQ) for older people. Br J Sports Med. 2010;44(14):1029-34. PMID: 19474003; https://doi.org/10.1136/bjsm.2009.060350.
24. Simões MDSM, Garcia IF, Costa LDC, Lunardi AC. Life-Space Assessment questionnaire: Novel measurement properties for Brazilian community-dwelling older adults. Geriatr Gerontol Int. 2018;18(5):783-9. PMID: 29372585; https://doi.org/10.1111/ggi.13263.
25. Dodds RM, Murray JC, Robinson SM, Sayer AA. The identification of probable sarcopenia in early old age based on the SARC-F tool and clinical suspicion: findings from the 1946 British birth cohort. Eur Geriatr Med. 2020;11(3):433-41. PMID: 32297269; https://doi.org/10.1007/s41999-020-00310-5.
26. Kim M, Won CW. Sarcopenia in Korean Community-Dwelling Adults Aged 70 Years and Older: Application of Screening and Diagnostic Tools From the Asian Working Group for Sarcopenia 2019 Update. J Am Med Dir Assoc. 2020;21(6):752-8. PMID: 32386844; https://doi.org/10.1016/j.jamda.2020.03.018.
27. Mo YH, Zhong J, Dong X, et al. Comparison of Three Screening Methods for Sarcopenia in Community-Dwelling Older Persons. J Am Med Dir Assoc. 2021;22(4):746-50.e1. PMID: 32669238; https://doi.org/10.1016/j.jamda.2020.05.041.
28. Yang M, Hu X, Xie L, et al. SARC-F for sarcopenia screening in community-dwelling older adults: Are 3 items enough? Medicine (Baltimore). 2018;97(30):e11726. PMID: 30045339; https://doi.org/10.1097/MD.0000000000011726.

29. Perkin O, McGuigan P, Thompson D, Stokes K. A reduced activity model: a relevant tool for the study of ageing muscle. Biogerontology. 2016;17(3):435-47. PMID: 26506931; https://doi.org/10.1007/s10522-015-9613-9.
30. Breen L, Stokes KA, Churchward-Venne TA, et al. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. J Clin Endocrinol Metab. 2013;98(6):2604-12. PMID: 23589526; https://doi.org/10.1210/jc.2013-1502.
31. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7(1):28-36. PMID: 27066316; https://doi.org/10.1002/jcsm.12048.
32. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748-59. PMID: 25241753; https://doi.org/10.1093/ageing/afu115.
33. Rolland Y, Dupuy C, Abellan Van Kan G, et al. Sarcopenia Screened by the SARC-F Questionnaire and Physical Performances of Elderly Women: A Cross-Sectional Study. J Am Med Dir Assoc. 2017;18(10):848-52. PMID: 28629717; https://doi.org/10.1016/j.jamda.2017.05.010.
34. Martone AM, Marzetti E, Salini S, et al. Sarcopenia Identified According to the EWGSOP2 Definition in Community-Living People: Prevalence and Clinical Features. J Am Med Dir Assoc. 2020;21(10):1470-4. PMID: 32359893; https://doi.org/10.1016/j.jamda.2020.03.007.
35. Brennan-Olsen SL, Vogrin S, Balogun S, et al. Education, occupation and operational measures of sarcopenia: Six years of Australian data. Australas J Ageing. 2020;39(4):e498-e505. PMID: 32969133; https://doi.org/10.1111/ajag.12816.
36. Christofoletti M, Duca GFD, Benedetti TRB, Malta DC. Sociodemographic determinants of multimorbidity in Brazilian adults and older adults: a cross-sectional study. Sao Paulo Med J. 2022;140(1):115-22. PMID: 35043867; https://doi.org/10.1590/1516-3180.2021.0105.R1.31052021.
37. Lustosa LP, Tavares CCA, Vital DKJC, et al. Risco de sarcopenia em idosas com queixa de dor lombar aguda. Fisioter Pesqui. 2018;25(3):260-8. https://doi.org/10.1590/1809-2950/17014525032018.
38. Jacobs JM, Hammerman-Rozenberg R, Cohen A, Stessman J. Chronic back pain among the elderly: prevalence, associations, and predictors. Spine (Phila Pa 1976). 2006;31(7):E203-7. PMID: 16582841; https://doi.org/10.1097/01.brs.0000206367.57918.3c.
39. Tzeng PL, Lin CY, Lai TF, et al. Daily lifestyle behaviors and risks of sarcopenia among older adults. Arch Public Health. 2020;78(1):113. PMID: 33292561; https://doi.org/10.1186/s13690-020-00498-9.
40. Smith L, Tully M, Jacob L, et al. The Association Between Sedentary Behavior and Sarcopenia Among Adults Aged ≥65 Years in Low- and Middle-Income Countries. Int J Environ Res Public Health. 2020;17(5):1708. PMID: 32151034; https://doi.org/10.3390/ijerph17051708.
41. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010. PMID: 26180873.
42. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451-62. PMID: 33239350; https://doi.org/10.1136/bjsports-2020-102955.
43. Kitamura A, Seino S, Abe T, et al. Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. J Cachexia Sarcopenia Muscle. 2021;12(1):30-8. PMID: 33241660; https://doi.org/10.1002/jcsm.12651.
44. Saraiva MD, Apolinario D, Avelino-Silva TJ, et al. The Impact of Frailty on the Relationship between Life-Space Mobility and Quality of Life in Older Adults during the COVID-19 Pandemic. J Nutr Health Aging. 2021;25(4):440-7. PMID: 33786560; https://doi.org/10.1007/s12603-020-1532-z.
45. de Lima MDCC, Perracini MR, Guerra RO, et al. Accuracy of the life-space mobility measure for discriminating frailty. Rev Bras Geriatr Gerontol. 2022;25(5):e210219. https://doi.org/10.1590/1981-22562022025.210219.pt
46. Kuspinar A, Verschoor CP, Beauchamp MK, et al. Modifiable factors related to life-space mobility in community-dwelling older adults: results from the Canadian Longitudinal Study on Aging. BMC Geriatr. 2020;20(1):35. PMID: 32005107; https://doi.org/10.1186/s12877-020-1431-5.
47. Rudnicka E, Napierała P, Podfigurna A, et al. The World Health Organization (WHO) approach to healthy ageing. Maturitas. 2020;139:6-11. PMID: 32747042; https://doi.org/10.1016/j.maturitas.2020.05.018.

Authors' contributions: Batista PP: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), and writing-original draft (equal); Perracini MR: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), and writing-review and editing (equal); de Amorim JSC: conceptualization (equal), formal analysis (equal), investigation (equal), methodology (equal), software (equal), and writing-review and editing (equal); de Lima MDCC: formal analysis (equal), investigation (equal), methodology (equal), visualization (equal), and writing-review and editing (equal); Lima CA: data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), software (equal), and writing-review and editing (equal); Pereira DS: conceptualization (equal), formal analysis (equal), investigation (equal), methodology (equal), supervision (equal), and writing-review and editing (equal); Dantas RG: data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), and visualization (equal); Fittipaldi EODS: formal analysis (equal), investigation (equal), methodology (equal), and visualization (equal); Santos AD: formal analysis (equal), investigation (equal), methodology (equal), and visualization (equal); Campos HLM: formal analysis (equal), investigation (equal), methodology (equal), and

visualization (equal); and Pereira LSM: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), supervision (equal) and writing-review and editing (lead). All authors approved the final version of the study and reserved public responsibility for its content

Remobilize Research Network Affiliations: Alexandre da Silva, Francis Trombini-Souza, Adriana Guedes Carlos, Juliana Maria Gazzola, Mirian Moreira, Paulo Henrique Silva Pelicioni, Mônica Beatriz Ferreira, Etiene Duim, Nayara Tasse de Oliveira Cirino, Renata dos Ramos Varanda, Suzana Albuquerque de Moraes, Guilherme Medeiros de Alvarenga, Cristina Cristovão Ribeiro da Silva, Renato Barbosa dos Santos, Sarah Giulia Bandeira Felipe, and Lygia Paccini Lustosa *(in memoriam)*

Sources of funding: No funding sources
Conflicts of interest: The authors declare no conflicts of interest

Date of first submission: March 24, 2022
Last received: July 18, 2022
Accepted: August 19, 2022

Address for correspondence:
Patricia Parreira Batista
Universidade Federal de Minas Gerais (UFMG)
Av. Pres. Antônio Carlos, 6.627
Pampulha — Belo horizonte (MG) — Brasil
CEP 31270-901
Tel. (+55 31) 34097395
E-mail: ppb@ufmg.br

Short-term outcomes of COVID-19 in pregnant women unvaccinated for SARS-CoV-2 in the first, second, and third trimesters: a retrospective study

Filiz Yarsilikal Guleroglu[I], Hatice Argun Atalmis[II], Icten Olgu Bafali[III], Gulser Bingol Dikdere[IV], Irfan Dikdere[V], Murat Ekmez[VI], Alpaslan Kaban[VII], Fatma Karasabanoglu[VIII], Busra Seker Atas[IX], Esra Selvi[X], Gulay Sumnu[XI], Merve Topaktas[XII], Merve Yasti Dayan[XIII], Sevilay Yavuz Dogu[XIV], Ali Cetin[XV]

Haseki Training and Research Hospital affiliated with Health Sciences University, Istanbul, Turkey

[I]MD. Perinatologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0003-4577-3368

[II]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0003-0432-8786

[III]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0003-4133-2477

[IV]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0003-3657-1182

[V]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0001-9604-3053

[VI]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0001-5045-3831

[VII]MD. Gynecologic Oncologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-3623-7240

[VIII]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-2768-8218

[IX]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-6190-3727

[X]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0003-0182-8988

[XI]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-8846-9123

[XII]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-8005-2876

[XIII]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-5863-1986

[XIV]MD. Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0001-6785-2089

[XV]MD, PhD. Perinatologist, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital affiliated with Health Sciences University, Sultangazi, Istanbul, Turkey.
https://orcid.org/0000-0002-5767-7894

KEY WORDS (MeSH terms):
COVID-19.
SARS-CoV-2.
Pregnancy.
Intensive care units.
Intensive care units, neonatal.

AUTHORS' KEY WORDS:
Outcome.
Computed tomography.
Intensive care unit.
Neonatal intensive care unit.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) may be asymptomatic or symptomatic in pregnant women. Compared to non-pregnant reproductive-aged women, symptomatic individuals appear to have a higher risk of acquiring severe illness sequelae.

OBJECTIVES: We assessed the clinical and laboratory characteristics and outcomes of pregnant COVID-19 patients unvaccinated for severe acute respiratory syndrome coronavirus 2 according to the trimester of pregnancy.

DESIGN AND SETTING: This was a retrospective observational study conducted in a tertiary-level hospital in Turkey.

METHODS: This retrospective study reviewed the clinical and laboratory characteristics and outcomes of 445 pregnant COVID-19 patients hospitalized during the first, second, and third trimesters of pregnancy and 149 other pregnant women as controls in a tertiary center from April 2020 to December 2021. All participants were unvaccinated.

RESULTS: Overall, the study groups were comparable in terms of baseline clinical pregnancy characteristics. There was no clear difference among the study participants with COVID-19 in the first, second, and third trimesters of pregnancy. However, a considerably high number of clinical and laboratory findings revealed differences that were consistent with the inflammatory nature of the disease.

CONCLUSIONS: The study results reveal the importance of careful follow-up of hospitalized cases as a necessary step by means of regular clinical and laboratory examinations in pregnant COVID-19 patients. With further studies, after implementing vaccination programs for COVID-19 in pregnant women, these data may help determine the impact of vaccination on the outcomes of pregnant COVID-19 patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a ribonucleic acid virus that causes coronavirus disease 2019 (COVID-19).[1,2] Within three months of the first case of COVID-19 being discovered at the end of 2019, the World Health Organization labeled the disease a pandemic.[3] Although most COVID-19 patients present with mild to moderate symptoms,[4] a small proportion of patients develop severe disease presentations, including respiratory failure, myocarditis, septic shock, and multiorgan failure.[5] Acute respiratory distress syndrome develops in up to one-third of individuals hospitalized with severe pneumonia.[6] Despite maximal cardiac support and invasive mechanical ventilation, mortality remains high in this population.[7,8]

Pregnant women comprise a distinct subgroup among those at increased risk of severe COVID-19 as these women are more sensitive to certain viral infections than the general population.[9] The pathogenesis of SARS-CoV-2 infection in pregnancy is yet unknown.[10] Affected pregnant women, like other COVID-19 patients, can be asymptomatic; however, they may also have several complications that worsen the outcome of their pregnancy. This is because during the course of their pregnancy, important pathophysiological deterioration can occur, including the development of increased pro-inflammatory states, cytokine production, and oxidative stress, all of which ultimately lead to cellular death.[11] According to some research data, the severity of

the illness in pregnant COVID-19 patients, is linked to perinatal risks and pregnancy outcomes.[12,13] Pregnant women with suspected or confirmed COVID-19 should receive comprehensive obstetric management as well as mental health and psychosocial support to avoid complications[14]; in addition, they should be encouraged to receive regular perinatal care.[15]

For large population-based studies, there is a need to shed light on the clinical presentations developed under the effects of the baseline health status of patients to assess how SARS-CoV-2 infection during pregnancy affects pregnancy outcomes how it results in *in-utero* vertical transmission. In 2021, the implementation of COVID-19 vaccination in pregnant women was initiated in Turkey. Many hospitalized pregnant women among the general COVID-19 patients could not receive vaccination during the pandemic. We believe that a review of the clinical characteristics and outcomes of pregnant women treated for COVID-19 will be useful in improving the medical care of pregnant COVID-19 patients in the future, especially in the different trimesters of pregnancy.

OBJECTIVE

This study aimed to assess the clinical and laboratory characteristics and outcomes of pregnant COVID-19 patients unvaccinated for SARS-CoV-2 during the first, second, and third trimesters of pregnancy.

METHODS

This retrospective study was designed to compare the clinical and laboratory characteristics and outcomes of hospitalized pregnant COVID-19 patients, many of whom were referred to our tertiary care center. In addition, those without COVID-19 were used as controls. This study was conducted at a tertiary center, including 445 pregnant COVID-19 patients and 149 pregnant women as controls, from April 2020 to December 2021. The COVID-19 patients were divided into three subgroups according to the hospitalization in the first, second, and third trimesters. In addition, the findings from a cohort of pregnant women with uncomplicated, healthy pregnancies in the third trimester between 30–41 weeks and who delivered during the same period were used as control data for comparison. COVID-19 infection was confirmed by positive polymerase chain reaction for SARS-CoV-2 in nasopharyngeal samples, and all study participants were unvaccinated for COVID-19. This study was approved by the health authorities and the Ethics Committee for Human Research of our institution (Haseki Training and Research Hospital Ethics Committee of Clinical Studies; date: February 09, 2022; Registry No: 19-2022). During the study period, pregnant COVID-19 patients were managed following the national health guidelines, including oxygen administration, use of antiviral drugs, hydroxychloroquine, steroids, antibiotics, thromboprophylaxis, and bronchodilators. In addition, respiratory support was provided through mechanical ventilation after admission to the intensive care unit (ICU) when required.

Regarding the participants' clinical characteristics, we collected the following data from the electronic patient records of our center: maternal age, gravidity, parity, ethnicity (native or Arabic), smoking status (yes or no), requirement of assisted reproductive technology for conception (yes or no), pre-pregnancy body mass index, mode of delivery (vaginal or cesarean), gestational age at the time of COVID-19 infection, gestational age at delivery, and maternal comorbidities (diabetes mellitus, hypertension, renal disease, asthma, and thyroid disease). In addition, in routine laboratory evaluation, hematological, biochemical, and inflammatory parameters were collected at admission, and maternal, fetal, and neonatal characteristics were recorded. A prophylactic dose of low molecular weight heparin was routinely prescribed for COVID-19 in our study population.

Statistical analysis

Data are presented as means, standard deviations, medians with minimum and maximum values, and counts with percentage values. IBM SPSS for Windows v25 (IBM SPSS, Armonk, New York, United States) was used for the descriptive and comparative analyses. After the normality test, data were analyzed using analysis of variance (ANOVA) or the Kruskal–Wallis ANOVA test with Tukey's or Mann–Whitney *U* tests, respectively. Next, categorical variables were analyzed using the chi-squared test. P values < 0.05 were considered statistically significant.

RESULTS

This retrospective study included 445 pregnant COVID-19 patients and 149 healthy pregnant women as controls. **Table 1** shows the clinical characteristics of pregnant women with and without COVID-19. Pregnant COVID-19 patients were divided into three groups according to the time of diagnosis in the first, second, and third trimesters. The rate of Arab immigrants in the control group was significantly higher than in the other groups ($P < 0.05$). In addition, the gestational age at delivery was significantly higher in the control group compared to the second-trimester participants ($P < 0.05$). There were no significant differences among the study groups regarding maternal age, gravidity, parity, pre-pregnancy body mass index, smoking status, use of assisted reproductive technology, mode of delivery, or maternal comorbidities ($P > 0.05$).

Table 2 shows the laboratory parameters of pregnant women with and without COVID-19. The median lymphocyte, platelet count, and blood urea nitrogen values were significantly higher in the controls and in the first-trimester participants compared to the second- and third-trimester participants ($P < 0.05$). The median

Table 1. Clinical characteristics of pregnant women with coronavirus disease 2019 (COVID-19) in the first, second, and third trimesters and of pregnant healthy controls

	Pregnant COVID-19 patients			Pregnant healthy controls	Significance
	First trimester (n = 45)	Second trimester (n = 120)	Third trimester (n = 280)	Thirdtrimester (n = 149)	
Maternal age (years)	29 (21–43)	30 (18–42)	29 (17–47)	28 (17–43)	NS
Gravidity	3 (1–9)	3 (1–10)	3 (1–9)	3 (1–12)	NS
Parity	1 (0–7)	1 (0–7)	1 (0–7)	2 (0–6)	NS
Ethnicity, n (%)					P = 0.001
Native	41 (91.1%)	111 (92.5%)	236 (84.3%)	106 (71.1%)	
Arabic	4 (8.9%)[a]	9 (7.5%)[a]	44 (15.7%)[a]	43 (28.9%)[b]	
Smoking, n (%)					NS
Yes	2 (4.4%)	2 (1.7%)	11 (3.9%)	2 (1.3%)	
No	43 (95.6%)	110 (98.3%)	269 (96.1%)	148 (98.7%)	
ART pregnancy, n (%)					NS
Yes	0 (0%)	4 (3.3%)	7 (2.5%)	2 (1.3%)	
No	45 (100%)	116 (96.7%)	273 (97.5%)	147 (98.7%)	
Pre-pregnancy BMI (kg/m²)	24.3 (20.1–26.2)	23.7 (21.3–27.4)	25.8 (22.4–37.3)	28.3 (19.9–45.7)	NS
Mode of delivery, n (%)					
Vaginal	22 (53.7%)	52 (44.4%)	109 (39.1%)	77 (52.7%)	NS
Cesarean	19 (46.3%)	65 (55.6%)	170 (60.9%)	69 (47.3%)	
Gestational age at diagnosis (weeks)	10 (6–14)	23 (15–28)	36 (29–42)		
Gestational age at delivery (weeks)	38 (34–40)[a,b]	38 (23–41)[b]	38 (30–42)[a,b]	38.5 (30–41)[a]	P = 0.001
Maternal comorbidities, n (%)					NS
DM	5 (11.1%)	5 (4.2%)	17 (6.1%)	9 (6%)	
HT	0 (0%)	3 (2.5%)	8 (2.9%)	11 (7.4%)	
Renal disease	0 (0%)	1 (0.8%)	2 (0.7%)	1 (0.7%)	
Asthma	2 (4.4%)	7 (5.8%)	10 (3.6%)	6 (4%)	
Thyroid disease	2 (4.4%)	12 (10%)	15 (5.4%)	7 (4.7%)	

ART = assisted reproductive technology; BMI = body mass index; DM = diabetes mellitus; HT = hypertension; NS = non-significant.
Data are presented as medians with minimum and maximum values or as counts with percentages and were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney *U* test for pairwise comparisons or the chi-square test as appropriate. Results of the pairwise comparisons were denoted with a letter ([a] or [b]). There was no significant difference between/among the study groups if they are marked with the same letter (P > 0.05), and there was a significant difference between/among the study groups if they are marked with different letters (P < 0.05).

platelet counts were significantly lower in the first-, second-, and third-trimester participants than that in the controls (P < 0.05). The median values of aspartate aminotransferase were significantly higher in the first-, second-, and third-trimester participants than that in the controls (P < 0.05). The mean values of hemoglobin and hematocrit were significantly higher in the first-trimester participants than those in the other groups (P < 0.05). The median white blood cell count was significantly higher in the control group than those in the other groups (P < 0.05). The median white blood cell counts were significantly higher in the third-trimester participants than those of the first- and second-trimester participants (P < 0.05). The median neutrophil count was significantly higher in the control group than those in the other groups (P < 0.05). The median neutrophil counts were significantly higher in the second- and third-trimester participants than that in the first-trimester participants (P < 0.05). The median C-reactive protein level was significantly lower in the control group than those in the other groups (P < 0.05). The median C-reactive protein values were significantly lower in the first-trimester participants than those of the second- and third-trimester participants (P < 0.05). The median ferritin values were significantly higher in the first- and second-trimester participants than that of the third-trimester participants (P < 0.05). Compared to the values of the other groups, the median creatinine values were significantly lower in the second-trimester participants (P < 0.05). The median alanine aminotransferase value was significantly lower in the control group than those in the other groups (P < 0.05). The median alanine aminotransferase values were significantly lower in the third-trimester participants than those of the first- and second-trimester participants (P < 0.05). The median lactate dehydrogenase values were significantly higher in the controls and in the third-trimester participants than those of the first- and second-trimester participants (P < 0.05). The median D-dimer levels were significantly higher in the third-trimester participants than those of the first- and second-trimester participants (P < 0.05). There were no significant differences in the monocyte and fibrinogen levels among

Table 2. Laboratory parameters of pregnant women with coronavirus disease 2019 (COVID-19) in the first, second, and third trimesters and of pregnant healthy controls

	Pregnant COVID-19 patients			Pregnant healthy controls	Significance
	First trimester (n = 45)	Second trimester (n = 120)	Third trimester (n = 280)	Thirdtrimester (n = 149)	
WBC (103 µL)	6.1 (2.6–22.3)[c]	7.5 (2.7–23.1)[c]	8.2 (3.2–20.8)[b]	10.7 (5.5–20.2)[a]	P = 0.001
NEU (103 µL)	4.1 (1.5–18.8)[c]	5.6 (0.9–21.6)[b]	6.3 (1.7–19.6)[b]	7.9 (3.7–20)[a]	P = 0.001
LYM (103 µL)	1.6 (0.3–3.1)[a]	1.2 (0.4–4.1)[b]	1.3 (0.2–3.8)[b]	1.8 (0.4–4.4)[a]	P = 0.001
MONO (103 µL)	0.4 (0.1–0.9)	0.4 (0.1–1.5)	0.4 (0.1–1.8)	0.5 (0.1–1.5)	NS
Hb (g/dL)	12.6 (8.8–14.8)[b]	11.1 (8.5–13.3)[a]	11.3 (5.6–15.6)[a]	11.6 (7–14.8)[a]	P = 0.001
Hct (%)	36.1 ± 3.4[b]	32.9 ± 3.1[a]	33.6 ± 3.8[a]	34.1 ± 3.9[a]	P = 0.001
PLT (103 µL)	207 (30–329)[b]	199 (67–412)[b]	197 (29–473)[b]	232 (110–441)[a]	P = 0.001
PCT (%)	0.2 (0.04–0.4)[a]	0.2 (0.07–0.38)[b]	0.2 (0.03–0.5)[b]	0.23 (0.09–0.41)[a]	P = 0.001
CRP (mg/L)	7.9 (0.3–159)[b]	31.7 (0.5–224)[c]	23.6 (0.7–197)[c]	3.4 (0.6–4.9)[a]	P = 0.001
Ferritin (ng/mL)	50 (10.7–778)[a]	50.9 (3.4–480)[a]	30.8 (3.5–900)[b]	-	P = 0.002
BUN (mg/dL)	15 (8–37)[a]	11.9 (5–77)[b]	11.3 (4.2–32)[b]	14 (9–31)[a]	P = 0.001
Creatinine (mg/dL)	0.46 (0.3–0.81)[a]	0.43 (0.25–2.38)[b]	0.46 (0.25–0.85)[a]	0.48 (0.34–0.72)[a]	P = 0.003
AST (IU/L)	24 (11–110)[b]	25 (8–169)[b]	22 (8–168)[b]	18 (12–35)[a]	P = 0.001
ALT (IU/L)	20.5 (8–145)[b]	16 (5–241)[b]	12 (4–222)[c]	11 (4–36)[a]	P = 0.001
Direct bilirubin (mg/dL)	0.1 (0.1–0.3)	0.2 (0.1–2.1)	0.2 (0.1–2.6)	-	NS
Indirect bilirubin (mg/dL)	0.2 ± 0.16	0.3 ± 0.16	0.3 ± 0.15	-	NS
Total bilirubin (mg/dL)	0.21 (0.1–0.7)	0.49 (0.2–2.1)	0.47 (0.2–2.7)	-	NS
LDH (IU/L)	190 (139–455)[b]	204 (100–679)[b]	236 (111–968)[a]	266 (244–481)[a]	P = 0.002
D-dimer (mg/L)	0.54 (0.3–33.9)[a]	1.1 (0.4–11.2)[a]	1.5 (0.3–36)[b]	-	P = 0.001
Fibrinogen (mg/dL)	410 (284–680)	437 (111–674)	446 (134–773)	559 (349–660)	NS
Maternal arterial pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	-	NS
Bicarbonate (mmol/L)	24 ± 0.4	22.7 ± 2.8	21.7 ± 4.1	-	NS

WBC = white blood cell count; NEU = neutrophil; LYM = lymphocytes; MONO = monocytes; Hb = hemoglobin; Hct = hematocrit; PLT = platelet; PCT = platelet crit; CRP = C-reactive protein; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; IU = international unit; NS = non-significant.

Parametric data are presented as means with standard deviations and were analyzed using an analysis of variance (ANOVA) test followed by Tukey's test for pairwise comparisons as appropriate. Non-parametric data are presented as medians with minimum and maximum values and were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney *U* test for pairwise comparisons as appropriate. The results of the pairwise comparisons were denoted with letters ([a], [b], or [c]). There was no significant difference between/among the study groups if they are marked with the same letter (P > 0.05), and there was a significant difference between/among the study groups if they are marked with different letters (P < 0.05).

the study groups (P > 0.05). There were no significant differences among the first-, second-, and third-trimester participants regarding the values of direct, indirect, and total bilirubin, maternal pH, and bicarbonate (P > 0.05).

The clinical presentations of pregnant women with and without COVID-19 are presented in **Table 3**. The rates of intrahepatic cholestasis of pregnancy and intrauterine growth restriction were significantly lower in the controls and third-trimester participants than those in the first- and second-trimester participants (P < 0.05). The rate of preeclampsia was significantly lower in the control group than those in the other groups (P < 0.05). The rates of preterm birth and preterm prelabor rupture of membranes were significantly lower in the controls and first-trimester participants than those in the second- and third-trimester participants (P < 0.05). The rate of placental abruption was significantly higher in the third-trimester participants than those in the other groups (P < 0.05). The rates of oligohydramnios were significantly higher in the first- and second-trimester participants than those in the third-trimester participants (P < 0.05). The median length of hospitalization was significantly higher in the COVID-19 participants than that in the controls (P < 0.05). The median lengths of hospitalization were significantly higher in the second- and third-trimester participants than those in the first-trimester participants (P < 0.05). The proportion of second-trimester COVID-19 participants without drug use was significantly higher than those of the first- and third-trimester participants (P < 0.05). More second-trimester participants were using antiviral drugs compared to the first- and third-trimester participants (P < 0.05). The proportions of COVID-19 participants with no computed tomography imaging data and who presented with pneumonia findings in their computed tomography imaging were significantly higher in those in their second- and third-trimesters than in those in their first-trimester (P < 0.05).

Table 3. Maternal, fetal, and neonatal characteristics of pregnant women with coronavirus disease 2019 (COVID-19) in the first, second, and third trimesters and of pregnant healthy controls

	Pregnant COVID-19 patients			Pregnant healthy controls	Significance
	First trimester (n = 45)	Second trimester (n = 120)	Third trimester (n = 280)	Third trimester (n = 149)	
Intrahepatic cholestasis of pregnancy, n (%)	2 (4.4%)[b]	7 (5.8%)[b]	2 (0.7%)[a]	1 (0.7%)[a]	P = 0.003
Preeclampsia, n (%)	9 (20%)[b]	19 (15.8%)[b]	34 (12.1%)[b]	4 (2.7%)[a]	P = 0.001
Preterm birth, n (%)	4 (8.9%)[a]	23 (19.2%)[b]	45 (16.1%)[b]	13 (8.7%)[a]	P = 0.048
PPROM, n (%)	0 (0 %)[a]	11 (9.2%)[b]	16 (5.7%)[b]	2 (1.3%)[a]	P = 0.009
Stillbirth, n (%)	0 (0 %)	4 (3.3%)	4 (1.4%)	4 (2.7%)	NS
Placental abruption, n (%)	0 (0%)	4 (3.3%)[a]	19 (6.8%)[b]	2 (1.3%)[a]	P = 0.02
Oligohydramnios, n (%)	4 (8.9%)[a]	12 (10%)[a]	17 (6.1%)[b]	0 (0%)	P = 0.002
IUGR, n (%)	5 (11.1%)[b]	16 (13.3%)[b]	20 (7.1%)[a]	2 (1.3%)[a]	P = 0.002
Length of hospitalization (days)	4 (1–13)[c]	6 (1–45)[b]	5 (1–45)[b]	2 (1–8)[a]	P = 0.001
Time from onset of symptoms to hospitalization (days)	2 (1–10)	2 (1–10)	2 (1–10)	-	NS
Disease severity, n (%)				-	NS
Mild	33 (73.3%)	79 (65.8%)	207 (73.9%)		
Moderate	12 (26.7%)	30 (25%)	55 (19.6%)		
Severe	0 (0%)	10 (8.3%)	15 (5.3%)		
Critical	0 (0%)	1 (0.8%)	3 (1.2%)		
Need for oxygen, n (%)				-	NS
No	27 (60%)	51 (42.5%)	158 (56.4%)		
Non-invasive	18 (40%)	63 (52.5%)	111 (39.6%)		
Mechanical ventilation	0 (0%)	6 (5%)	11 (4%)		
Treatment, n (%)				-	P = 0.03
No drugs	28 (62.2%)[a]	49 (40.8%)[b]	158 (56%)[a]		
Steroids	3 (6.7%)	15 (12.5%)	28 (10.1%)		
Chloroquine	1 (2.2%)	4 (3.3%)	20 (7.2%)		
Antiviral drugs	10 (22.2%)[a]	40 (33.3%)[b]	58 (20.9%)[a]		
Steroids plus antiviral drugs	3 (6.7%)	12 (10%)	16 (5.8%)		
CT imaging, n (%)				-	P = 0.003
No CT imaging	44 (97.8%)[a]	103 (85.8%)[b]	212 (75.7%)[b]		
No diagnosis of pneumonia on CT	0 (0%)	1 (0.8%)	12 (4.2%)		
Diagnosis of pneumonia on CT	1 (2.2%)[a]	16 (13.3%)[b]	56 (20.1%)[b]		
Admission to the ICU, n (%)	0 (0%)	8 (6.7%)	18 (6.5%)	-	NS
Admission to the ICU in terms of hospitalization (days)	None	2 (1–3)	3 (1–8)	-	NS
Length of stay in the ICU (days)	None	6 (2–43)	6 (1–30)	-	NS
Mortality, n (%)	0 (0%)	2 (1.7%)	3 (1.1%)	-	NS
Birth weight (g)	2700 (2645–3030)	3110 (670–3950)	3121 (1578–4248)	3227 (1438–4410)	NS
Apgar score					NS
At 1 minute	9 (8–9)	9 (5–9)	9 (1–9)	9 (5–9)	
At 5 minutes	10 (9–10)	10 (8–10)	10 (3–10)	10 (6–10)	
Cord blood pH	7.4 (7.32–7.41)	7.32 (7.25–7.43)	7.35 (7.15–7.56)	7.35 (7.1–7.57)	NS
Need for NICU admission, n (%)	4 (8.9%)[a]	20 (16.7%)[a]	113 (40.4%)[b]	46 (30.9%)[b]	P = 0.001

PPROM = preterm prelabor rupture of membranes; IUGR = intrauterine growth restriction; CT = computed tomography; ICU = intensive care unit; NICU = neonatal intensive care unit; NS = non-significant.

Data are presented as medians with minimum and maximum values or as counts with percentages and were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney *U* test for pairwise comparisons or the chi-square test as appropriate. Results of the pairwise comparisons were denoted with a letter ([a] or [b]). There was no significant difference between/among the study groups if they are marked with the same letter (P > 0.05), and there was a significant difference between/among the study groups if they are marked with different letters (P < 0.05).

The proportions of the controls and COVID-19 participants in their third-trimester requiring admission to neonatal ICUs were significantly higher than those of the COVID-19 participants in their first- and second-trimesters ($P < 0.05$). There were no significant differences among the study groups in terms of stillbirth rates, birth weights, Apgar scores at 1 and 5 min, and cord blood pH values ($P > 0.05$). There were no significant differences among the pregnant COVID-19 patients in the first-, second-, and third-trimesters in terms of rates of disease severity, the need for oxygen, admission to the ICU, mortality, time from onset of symptoms to hospitalization, admission to the ICU, and length of stay in the ICU ($P > 0.05$). Among all pregnant COVID-19 patients, there was no significant difference in the severity of COVID-19 among pregnant women with comorbidities ($P > 0.05$).

DISCUSSION

This study examined the clinical and laboratory findings and outcomes of pregnant COVID-19 patients hospitalized in the first, second, and third trimesters. In addition, the clinical and laboratory parameters and maternal, fetal, and neonatal outcomes of the study groups were compared. The statistical analysis revealed no clear difference among the pregnant women who developed COVID-19 in the first, second, and third trimesters. However, some obstetric complications were seen specifically in some of the first-, second-, and third-trimester participants that were in accordance with the nature of obstetric complications, including intrahepatic cholestasis of pregnancy, preeclampsia, preterm birth, preterm prelabor rupture of membranes, placental abruption, oligohydramnios, and intrauterine growth restriction.

In a recent study evaluating the clinical and laboratory data of pregnant COVID-19 patients who did not have any comorbid conditions, some severe clinical symptoms were observed in the third-trimester patients. Additionally, the need for intensive care, the rates of cesarean section delivery, and the rates of preterm delivery were all elevated among pregnant women.[16] In our study, participants with comorbidities were also included, and we found no significant difference among the pregnant COVID-19 patients in the first, second, and third trimesters in terms of rates of disease severity, admission to the ICU, and mode of delivery. However, in our study, the preterm birth rate was significantly higher in the first-trimester participants than in those diagnosed in the second and third trimesters.

Many studies have examined the laboratory characteristics of COVID-19 patients.[17–19] Sun et al. analyzed the blood examination results between pregnant COVID-19 patients and non-COVID-19 pregnant women.[20] They observed that pregnant COVID-19 patients had significantly fewer lymphocytes, significantly more neutrophils, and significantly higher C-reactive protein levels than controls. Chen et al. reported that 51 out of 116 pregnant women diagnosed with COVID-19 had lymphopenia,[21] while Liu et al. reported that 12 out of 15 pregnant COVID-19 patients had decreased lymphocyte counts and 10 out of 15 had higher C-reactive protein levels.[22] It has been suggested that pregnant COVID-19 patients' blood parameters be closely monitored, and variations in these inflammatory indices have been linked to patient prognoses.[21]

Thrombocytopenia occurs in 5–40% of non-pregnant COVID-19 patients.[23] The virus may directly infect bone marrow cells, or the immune system may aggregate and destroy platelets, thereby increasing platelet consumption via microthrombi production.[24] In a study that included 21 COVID-19 patients in the second and third trimesters of pregnancy and 48 patients without COVID-19, those with COVID-19 had higher platelet counts and lower fibrinogen levels than those without COVID-19.[25] This group also had lower platelet levels compared to the controls; however, there was no significant difference among the study groups regarding fibrinogen levels.

Several investigations have found that COVID-19 patients had abnormal aminotransferase levels.[26-28] According to a cohort analysis of 1,099 COVID-19 cases, 21.3% had elevated alanine aminotransferase levels, and 22.2% had elevated aspartate aminotransferase levels.[17] In our COVID-19 participants, elevated aspartate aminotransferase and alanine aminotransferase levels were also observed. This outcome could be attributed to the toxicity of the medications used during hospitalization as well as the clinical progression of the disease.

Numerous studies and meta-analyses have previously been published on the maternal and perinatal effects of the COVID-19 pandemic.[29,30] Notably, our findings are consistent with previous research indicating that pregnant women that are positive for COVID-19 may experience worse maternal and neonatal outcomes.[31,32] Simon et al. performed a cohort study to ascertain the effect of maternal COVID-19 on prematurity and obstetric outcomes.[33] Their study highlighted that COVID-19 is associated with obstetric complications such as preeclampsia, diabetes mellitus, prematurity, and cesarean delivery. Although the results of our study are in accordance with those of the aforementioned study, the cesarean section rates did not increase in our population.

Tunc et al. evaluated the clinical and laboratory findings of pregnant COVID-19 patients in all trimesters of pregnancy. In their study population, the ICU admission rates of the study groups were in accordance with the findings of our study.[34] We believe that managing hospitalized pregnant COVID-19 patients with a focus on monitoring clinical and laboratory findings and executing appropriate interventions could be a determining factor in reducing ICU admission rates.

Patients with mild-to-moderate SARS-CoV-2 infection, both symptomatic and asymptomatic, can recover within 7–14 days. According to the current statistics, the COVID-19 recovery rate

differs across countries. Because all COVID-19 cases comprise both symptomatic and asymptomatic cases, with 90% of symptomatic patients having mild to moderate symptoms, it is estimated that more than 80% of all COVID-19 cases can be handled with minimal or no medical intervention. The effectiveness of inpatient or critical care, as well as the patient's immune responses and baseline health status, determines recovery in the remaining cases.

The clinical circumstances of pregnant COVID-19 patients can rapidly deteriorate and result in respiratory failure. Therefore, meticulous follow-up of hospitalized cases is required, including monitoring of clinical and laboratory examination findings and performing therapeutic approaches. Changes in the cardiovascular system during pregnancy, such as increased heart rate, oxygen consumption, and decreased lung capacity, increase the risk of developing and progressing to severe acute respiratory distress syndrome. According to some studies, individuals may also exhibit signs and symptoms associated with effects on other organs.

Currently, no routine biomarkers for SARS-CoV-2 have been validated; however, several candidates are possible. The measurement of various general biomarkers in individuals with COVID-19 may aid in determining the severity of the disease and the efficacy of any treatments provided, particularly in patients with previous disorders linked to chronic conditions. Procalcitonin and C-reactive protein levels have been found to increase in various illness states, though not in all patients. Even if routine coagulation tests have low specificity for many infectious coagulation-related disturbances, they are not useless in the setting of COVID-19, especially when performing risk stratification in patients.

Taken together, the results of the relevant studies are in accordance with the findings of the current study. There are some contradictory results to those of previous studies, indicating the meaningful influence of pregnancy trimesters on the clinical presentations and outcomes of pregnant COVID-19 patients. The absence of a clear-cut difference among our study groups at the different trimesters of pregnancy may be due to the sample of our study, as it mainly consisted of COVID-19 participants who did not receive antenatal care from our center previously. In addition, the interpretation of our data requires caution, as there may be other undefined mechanisms linking COVID-19 to obstetrical outcomes in those with normal and pathologic conditions. There may be confounding factors associated with the range of gestational age in our study population, including confounding clinical factors such as maternal body mass index status, fetal sex, ethnicity, and the presence of undefined maternal infective and/or inflammatory states, as well as other systemic disorders. The inclusion of only healthy third-trimester pregnant women as controls may be considered a limiting factor from which to draw conclusions regarding the laboratory parameters of the current study. As a national strategy and part of the organization of the public health infrastructure, the assignment of COVID-19 patients to tertiary care hospitals, specifically the hospitalization of COVID-19 patients and compilation of experience in order to fight the challenges of severe complications, had a significant impact on reducing the morbidity and mortality and reducing the long-term sequelae of the condition.

CONCLUSION

In conclusion, no clinical and laboratory parameters clearly demonstrated worse outcomes in this review of hospitalized and unvaccinated pregnant COVID-19 patients. Overall, the clinical and laboratory data from the current examination, in accordance with the piling results of clinical COVID-19 studies, support the importance of careful follow-up and management of hospitalized pregnant COVID-19 patients by experienced healthcare workers, including regular clinical and laboratory examinations. This review also supports the value of a management strategy conducted in accordance with the versatile involvement of several organ systems in order to discharge pregnant COVID-19 patients with acceptable outcomes similar to non-pregnant COVID-19 patients. With further studies following the implementation of vaccination programs for COVID-19 in pregnant women, these data may help determine the impact of vaccination on the outcomes of pregnant COVID-19 patients.

REFERENCES

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141-54. Erratum in: Nat Rev Microbiol. 2022;20(5):315. PMID: 33024307; https://doi.org/10.1038/s41579-020-00459-7.
2. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front Microbiol. 2021;12:698169. PMID: 34248921; https://doi.org/10.3389/fmicb.2021.698169.
3. AlTakarli NS. China's Response to the COVID-19 Outbreak: A Model for Epidemic Preparedness and Management. Dubai Med J. 2020;3:44-9. https://doi.org/10.1159/000508448.
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. PMID: 32091533; https://doi.org/10.1001/jama.2020.2648.
5. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China, 2020. China CDC Wkly. 2020;2(8):113-22. PMID: 34594836.
6. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. Erratum in: JAMA. 2021;325(11):1113. PMID: 32031570; https://doi.org/10.1001/jama.2020.1585.

7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. Erratum in: Lancet. 2020;395(10229):1038. PMID: 32171076; https://doi.org/10.1016/s0140-6736(20)30566-3.
8. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020;382(21):2012-22. PMID: 32227758; https://doi.org/10.1056/nejmoa2004500.
9. Racicot K, Mor G. Risks associated with viral infections during pregnancy. J Clin Invest. 2017;127(5):1591-9. PMID: 28459427; https://doi.org/10.1172/jci87490.
10. Bloise E, Zhang J, Nakpu J, et al. Expression of severe acute respiratory syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-fetal interface in pregnancies complicated by preterm birth or preeclampsia. Am J Obstet Gynecol. 2021;224(3):298.e1-298.e8. PMID: 32853537; https://doi.org/10.1016/j.ajog.2020.08.055.
11. Marín R, Pujol FH, Rojas D, Sobrevia L. SARS- CoV-2 infection and oxidative stress in early-onset preeclampsia. Biochim Biophys Acta Mol Basis Dis. 2022;1868(3):166321. PMID: 34920081; https://doi.org/10.1016/j.bbadis.2021.166321.
12. Metz TD, Clifton RG, Hughes BL, et al. Disease Severity and Perinatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2021;137(4):571-80. PMID: 33560778; https://doi.org/10.1097/aog.0000000000004339.
13. Liu H, Wang LL, Zhao SJ, et al. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122. PMID: 32244166; https://doi.org/10.1016/j.jri.2020.103122.
14. Kakaraparthi VN, Alshahrani MS, Reddy RS, et al. Anxiety, depression, worry, and stress-related perceptions among antenatal women during the COVID-19 pandemic: Single group repeated measures design. Indian J Psychiatry. 2022;64(1):64-72. PMID: 35400735; https://doi.org/10.4103%2Findianjpsychiatry.indianjpsychiatry_1359_20.
15. Boelig RC, Saccone G, Bellussi F, Berghella V. MFM guidance for COVID-19. Am J Obstet Gynecol MFM. 2020;2(2):100106. PMID: 32363335; https://doi.org/10.1016/j.ajogmf.2020.100106.
16. Bozkurt F, Çoşkun Ö, Yeleç S, et al. Comparison of the Clinical and Laboratory Findings in COVID-19 Positive Pregnants without Comorbidity. Turk J Med Sci. 2021. PMID: 34233388; https://doi.org/10.3906/sag-2105-116. Epub ahead of print.
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. PMID: 32109013; https://doi.org/10.1056/nejmoa2002032.
18. Valapala VNG, Dasari N, Kolli VK, Mandapaka M. Clinical and biochemical profile of COVID-19 patients admitted in a tertiary care hospital in Visakhapatnam, India during post unlock 2.0 - a retrospective study. J Med Life. 2022;15(2):264-8. PMID: 35419104; https://doi.org/10.25122/jml-2021-0341.
19. Suryawanshi SY, Priya S, Sinha SS, et al. Dynamic profile and clinical implications of hematological and immunological parameters in COVID-19 patients. A retrospective study. J Family Med Prim Care. 2021;10(7):2518-23. PMID: 34568129; https://doi.org/10.4103/jfmpc.jfmpc_2400_20.
20. Sun G, Zhang Y, Liao Q, Cheng Y. Blood Test Results of Pregnant COVID-19 Patients: An Updated Case-Control Study. Front Cell Infect Microbiol. 2020;10:560899. PMID: 33117727; https://doi.org/10.3389/fcimb.2020.560899.
21. Chen L, Li Q, Zheng D, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. N Engl J Med. 2020;382(25):e100. PMID: 32302077; https://doi.org/10.1056/nejmc2009226.
22. Liu D, Li L, Wu X, et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. AJR Am J Roentgenol. 2020;215(1):127-32. Erratum in: AJR Am J Roentgenol. 2020;215(1):262. PMID: 32186894; https://doi.org/10.2214/ajr.20.23072.
23. Larsen JB, Pasalic L, Hvas AM. Platelets in Coronavirus Disease 2019. Semin Thromb Hemost. 2020;46(7):823-5. PMID: 32356294; https://doi.org/10.1055/s-0040-1710006.
24. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020;99(6):1205-8. PMID: 32296910; https://doi.org/10.1007/s00277-020-04019-0.
25. Ciavarella A, Erra R, Abbattista M, et al. Hemostasis in pregnant women with COVID-19. Int J Gynaecol Obstet. 2021;152(2):268-9. PMID: 33245783; https://doi.org/10.1002/ijgo.13499.
26. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020;73(3):566-74. PMID: 32298767; https://doi.org/10.1016/j.jhep.2020.04.006.
27. Bertolini A, van de Peppel IP, Bodewes FAJA, et al. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. Hepatology. 2020;72(5):1864-72. PMID: 32702162; https://doi.org/10.1002/hep.31480.
28. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. United European Gastroenterol J. 2020;8(5):509-19. PMID: 32450787; https://doi.org/10.1177/2050640620924157.
29. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. Lancet Glob Health. 2021;9(6):e759-e772. PMID: 33811827; https://doi.org/10.1016/s2214-109x(21)00079-6.
30. Khalil A, von Dadelszen P, Draycott T, et al. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. JAMA. 2020;324(7):705-6. PMID: 32648892; https://doi.org/10.1001/jama.2020.12746.
31. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020;369:m2107. PMID: 32513659; https://doi.org/10.1136/bmj.m2107.

32. Antoun L, Taweel NE, Ahmed I, Patni S, Honest H. Maternal COVID-19 infection, clinical characteristics, pregnancy, and neonatal outcome: A prospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2020;252:559-62. PMID: 32732059; https://doi.org/10.1016/j.ejogrb.2020.07.008.
33. Simon E, Gouyon JB, Cottenet J, et al. Impact of SARS-CoV-2 infection on risk of prematurity, birthweight and obstetric complications: A multivariate analysis from a nationwide, population-based retrospective cohort study. BJOG. 2022;129(7):1084-94. PMID: 35253329; https://doi.org/10.1111/1471-0528.17135.
34. Tunç Ş, Göklü MR, Oğlak SC. COVID-19 in pregnant women: An evaluation of clinical symptoms and laboratory parameters based on the 3 trimesters. Saudi Med J. 2022;43(4):378-85. PMID: 35414616; https://doi.org/10.15537/smj.2022.43.4.20210904.

Authors' contributions: Guleroglu FY: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Atalmis HA: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Bafali IO: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Dikdere GB: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Dikdere I: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Ekmez M: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Kaban A: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Karasabanoglu F: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Atas BS: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Selvi E: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Sumnu G: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Topaktas M: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Dayan MY: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); Dogu SY: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal); and Cetin A: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal) and writing-original draft (equal). All authors actively contributed to the discussion of the study results, and reviewed and approved the final version of the manuscript

Acknowledgments: This work, as a humble gesture of respect and appreciation, is wholeheartedly dedicated to all healthcare professionals worldwide who worked tirelessly to save the lives of COVID-19 patients and who shared their experiences to restrain the overwhelming COVID-19 pandemic.

Sources of funding: The authors declare that this study had no financial support.
Conflicts of interest: The authors declare that there are no conflicts of interest

Date of first submission: May 13, 2022
Last received: July 7, 2022
Accepted: August 19, 2022

Address for correspondence:
Filiz Yarsilikal Guleroglu
Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Health Sciences University
Sultangazi, Istanbul, Turkey
Tel. 905309682476
E-mail: filizyarsilikal@gmail.com

Body image in children and adolescents diagnosed with the human immunodeficiency virus: a systematic review

Suellem Zanlorenci[I], Andressa Ferreira da Silva[II], Diego Augusto Santos Silva[III]

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

Faculty of Health Sciences, Universidad Autónoma de Chile, Providencia, Chile

[I]BSc. Master Student, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
https://orcid.org/0000-0002-7476-5511

[II]MSc. Doctoral Student, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
https://orcid.org/0000-0002-8154-5664

[III]MSc, PhD. Associate Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil; and Associate Researcher, Faculty of Health Sciences, Universidad Autónoma de Chile, Providencia, Chile.
https://orcid.org/0000-0002-0489-7906

KEYWORDS (MeSH terms):
Body dissatisfaction.
Body composition.
Body image.
Child health.
Adolescent health.
HIV.

AUTHORS' KEYWORDS:
Body satisfaction.
Children.
Teenager.

ABSTRACT

CONTEXT: The relationship with body image, which is the way the body presents itself to each subject, can be aggravated in children and adolescents diagnosed with an human immunodeficiency virus (HIV) infection, since these patients use antiretroviral therapy and may suffer from the adverse effects of the treatment due to continuous use of medication.

OBJECTIVE: To estimate the prevalence of body image dissatisfaction, to describe the assessment methods, and to identify associated factors in children and adolescents diagnosed with HIV.

DESIGN AND SETTING: This is a systematic review. Department of Physical Education, Florianópolis - Brazil

METHODS: We followed the procedures of the Preferred Reporting Items for Systematic Reviews (PRISMA) and the Cochrane recommendations in the selection of articles through a search performed in eight databases.

RESULTS: Prevalence of body image dissatisfaction due to thinness was between 36.7–52.0% in males and 28.1–36.4% in females, and body image dissatisfaction due to overweight was between 8.0–31.2% in males and 21.9–50.0% in females. Factors associated with body image dissatisfaction were as follows: female sex, older age, low levels of physical activity, low self-esteem, higher body fat, higher body weight, greater arm muscle area, triceps skinfold thickness, and higher body mass index.

CONCLUSION: Children and adolescents of both sexes diagnosed with HIV infection are dissatisfied by thinness and overweight of their body image.

REGISTRATION: https://www.crd.york.ac.uk/prospero/ (CRD42021257676).

INTRODUCTION

The bodily manifestations related to the human immunodeficiency virus (HIV) and its treatment with antiretroviral therapy (ART) negatively affect not only the physical but also the psychological health of children and adolescents diagnosed with HIV infection; including body image issues.[1-5] Morphological changes related to lipodystrophy include loss of fat normally located in the face, buttocks, and extremities (lipoatrophy), contributing to perceived thinness, or gains of fat in the breasts, abdomen, and neck (lipohypertrophy), contributing to perceived overweight.[1,2,5,6] Children and adolescents with HIV infection are at risk of dissatisfaction with their body image (i.e., the way the body is presented to each child).[3-5] Furthermore, in children and adolescents without an HIV diagnosis, body image can be influenced by numerous physical, psychological, environmental, and cultural factors as determined subjectively by each child, and these may include the child's sex, age, media, beliefs, race, and general values, all of which also apply to children and adolescents diagnosed with HIV infection.[3-5]

Body image is a unique, dynamic, and multifaceted construction. Self-report body image assessment tools can take many forms, including questionnaires and scales with silhouettes, photos, or videos that represent stimuli with which respondents can compare and evaluate themselves.[7] The choice of an assessment instrument by an investigator should take into account the age group that will be assessed, the nature of the assessment method, and the psychometric properties of the instrument (eg, reliability and validity for the population and uses for the investigator).[9]

As noted above, assessing the body image of children and adolescents diagnosed with HIV infection is made important by the types of symptoms and medication (i.e., continuous ART) side effects that may redefine body contours and self-perceptions of these patients.[3-5] Conducting a

systematic review can capture, recognize, and synthesize scientific evidence to support proposals for qualified health practices and implement evidence-based practice.[8] In addition, the systematic review has a rigorous methodology proposed to identify studies on a topic in question, applying explicit and systematized search methods that assess the quality and validity of these studies.[8] In this sense, with the absence of a cure for chronic diseases such as HIV infection, the study of body image in children and adolescents diagnosed with it can help to understand the subgroups most likely to be dissatisfied with their body image.[10] Body image assessment tools can be critically important for directing the distribution of resources and implementing a variety of health programs to address physical, psychological, and social aspects of care for these patients.[11]

OBJECTIVE

Our aims were to systematically review the existing scientific literature in this area to estimate the prevalence of dissatisfaction with body image, to describe the assessment methods, and to identify associated factors in children and adolescents diagnosed with HIV infection.

METHODS

The report of this review is in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA)[12] and follows the recommendations of the Cochrane Collaboration Handbook[13] to answer the following question: what does the literature include about the prevalence, associated factors, and methods for assessing body image in children and adolescents diagnosed with HIV infection? The protocol for this study was registered in the PROSPERO database (registration number: CRD42021257676).

Search strategy, descriptors and keywords

The search was performed in the following databases: 1) PubMed via National Library of Medicine (MEDLINE); 2) Web of Science; 3) Scopus; 4) SPORTDiscus via EBSCOhost; 5) LILACS via Virtual Health Library; 6) Scientific Electronic Library Online (SciELO); 7) PsycINFO via the American Psychological Association (APA); and 8) Cumulative Index to Nursing and Allied Health Literature (CINAHL), via EBSCOhost.

The search for articles in databases was performed using the advanced search tool, based on the construction of blocks of descriptors and keywords related to the theme. The selection of descriptors was performed by consulting the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS)[14] platforms related to the PECO acromion (patient/population, exposure, comparison, and outcome). Keywords were also selected through consensus in published sources (original articles). Depending on the database, keywords and descriptors were entered in Portuguese, English, and/or Spanish.

The first block (outcome) was composed of terms referring to body image, the second block was composed of the population of interest (children and adolescents), and the third block was composed of the term related to HIV (**Appendix 1**).

The "OR" Boolean operator was used to add at least one keyword or descriptor of each block in the advanced search and the "AND" operator to relate the blocks of keywords/descriptors to each other. In addition, quotation marks ("") were used in compound words and to search for exact terms or expressions. Parentheses were used to combine search terms by outcome, exposure, and population categories. Asterisk (*) was used to search for all words derived from the same prefix.

The search was carried out in June 2021, considering all articles published up to this date. Additionally, the reference lists of eligible studies and those related to the topic of this review were manually searched to find possible relevant studies.

Eligibility criteria

Inclusion criteria were as follows: (a) population composed of children and/or adolescents (aged 0–19 years or with average age of up to 19 years) with diagnosis of HIV infection; (b) cross-sectional, longitudinal case-control studies, cohort studies, interventions, or randomized clinical trials that allowed extracting information about the body image of children and adolescents diagnosed with HIV infection. The study had the following exclusion criteria: theses, dissertations, monographs, abstracts, book chapters, point of view and review articles, validation and/or reproducibility articles, articles to determine cutoff points, and articles that did not present data classifying individuals according to body image. However, these publications were screened (available text and references) to find complete articles of interest to this review.

Selection of studies

Two independent reviewers (SZ and AFS) examined each database to obtain potential articles; duplicate articles were excluded and then other articles were excluded after the reading of titles and abstracts. Subsequently, the texts of selected articles were read in full for the selection of studies. A literature search was carried out in the references of the selected studies to select possible articles eligible for this review, not identified in the systematic search in databases. Disagreements between the two reviewers were resolved by a consensus meeting. A third reviewer (DASS) was consulted for unresolved disagreements.

The Zotero bibliographic manager version 5.0 (Roy Rosenzweig Center for History and New Media, Fairfax, Virginia, United States) was used to create specific libraries, which enabled the identification

and exclusion of duplicate articles, and division and organization of the results of each database.

Data extraction

Data were extracted by two independent reviewers (SZ and AFS) and consistency between them was checked by a third reviewer (DASS). The following information was extracted: names of authors, year of publication, methodological quality score, study site, age group investigated, population and sample, study design, stratification, test used to assess body image (example: scale of silhouettes, questionnaires, weight perception, etc.), prevalence, and associated factors.

Risk of Bias

The risk of bias/methodological quality of selected articles was assessed by two independent researchers (SZ and AFS). For cases of disagreement between the two, the third researcher (DASS) with experience in systematic review was consulted through a consensus meeting. To assess the risk of bias, a tool proposed by the National Heart, Lung and Blood Institute (NIH)[15] was used, according to the type of study. For cross-sectional and longitudinal studies, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)[15] is the recommended tool to assist in the assessment of internal validity (potential selection risk, information, measurement, or confounding factors) of cross-sectional and cohort studies.

Each question was scored with "0" or "1", "0" being applied to questions answered with "no" and "1" for those answered with "yes" or "not applicable". The "not applicable" option was used when it was not possible to evaluate one of the instrument's criteria due to the type of study (such as those with a cross-sectional design). The total score was obtained by summing the score of each question (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).[15]

RESULTS

In total, 2,083 articles were found; however, 166 were duplicates, resulting in 1,917 articles. After reading titles and abstracts, 1,884 studies were excluded because they did not meet the eligibility criteria, then 33 articles were read in full. Of these, four were included because they met the eligibility criteria.[3-5,16] Subsequently, the references of included articles were read, but no new articles were included in this review (**Figure 1**).

Of the four included studies, three were carried out in Brazil[3-5] and one in the United States of America.[16] The population evaluated

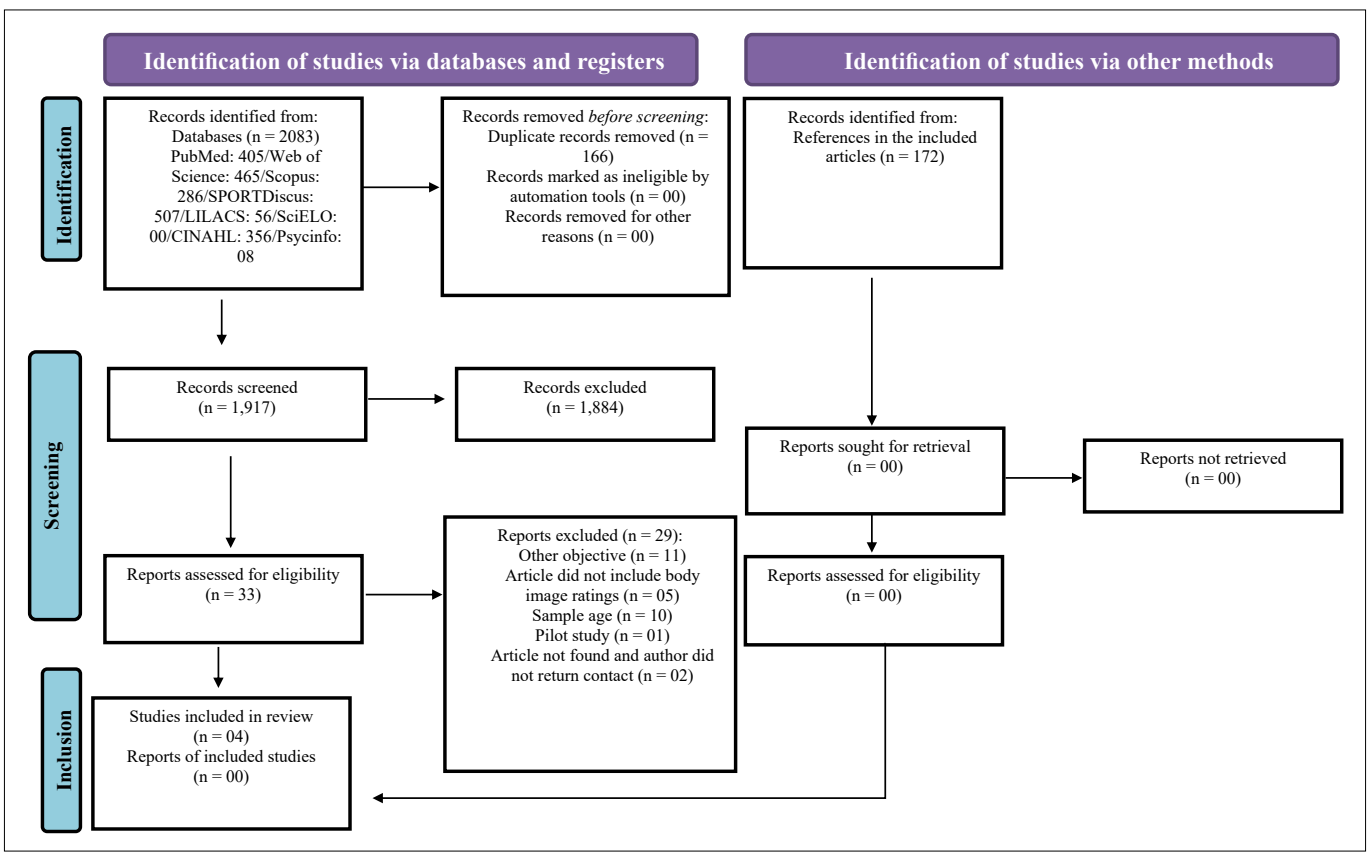


Figure 1. Flowchart of search, selection, and exclusion of articles.

comprised a total of 455 individuals of both sexes. Of studies that used samples stratified by sex, there were a total of 89 females and 71 males,[3-5] one study did not present stratification by sex.[16] All studies had cross-sectional design[3-5,16] (**Table 1**).

Of the four included articles, three aimed to present the prevalence of body image dissatisfaction.[3-5] In addition, the study by Alves Junior et al.[3] also tested the association between body image and total fat mass, body composition (skinfolds), bone age, moderate to vigorous physical activity, viral load, and antiretroviral therapy.[3] The study by Augustemak de Lima et al.[4] tested the association between body image and body composition (body mass index [BMI], skinfolds, and circumferences), age, sex, and economic level.[4] One study aimed at correlating body image (satisfied and dissatisfied) with self-esteem, physical activity, fat, and age[16] (**Table 2**).

Regarding the instruments used to assess body image and the form of classification, two studies used the silhouette scale previously validated with adolescents from Florianópolis, Brazil,[17] in which children and adolescents were classified as "satisfied with their body image", "want to reduce body weight", or "want to increase body weight".[3,4] One study used the Dusek's Secord-Jourard Body Cathexis Scale (1983), in which body image was classified using scores that resulted in three categories: "I do not like my body", "neutral", and "positive feelings".[16,18] One study used the silhouette scale validated by Kakeshita et al.,[19] classifying children and

Table 1. Description of studies on body image in children and adolescents diagnosed with human immunodeficiency virus (HIV) infection

Author(s), place and year	Outline	Population/Sample	Age group	Viral Load/ART/Stage of the disease
"AIDS among children--United States, 1996.[16] Division of HIV/AIDS Prevention, CDC", New York, Florida, New Jersey, California, Puerto Rico and Texas, United States (1997)	Cross-sectional study*	295 adolescents	13 to 15 years	Viral Load: NR ART: NR Stage of the disease: NR
Alves Junior et al.,[3] Florianópolis (SC), Brasil (2021)	Cross-sectional study	65 chidren and adolescents ♂: 30 ♀: 35	8 to 15 years	Viral Load: Average ♂: 2.2(1.0) Average ♀:2.1 (0.9) ART: With Protease Inhibitor: ♂: n = 19 (48.7%); ♀: n = 20 (51.3%) Without Protease Inhibitor: ♂: n = 06 (40.0%); ♀: n = 09 (60.0%) Do not use: ♂: n = 05 (45.5%); ♀: n = 06 (54.5%) Disease stage: NR
Augustemak de Lima et al.,[4] Florianópolis (SC), Brasil (2018)	Cross-sectional study	111 adolescents 57 living with HIV ♂: 25 ♀: 32 54 comparisons ♂: 26 ♀: 28	10 to 15 years	Viral charge: The absolute and relative count of CD4 + T lymphocytes was 791.3 cells.mm -3 e 30.4%, respectively (SD = 280.7 cells.mm -3 and 7.5%, respectively). An adolescent living with HIV had an undetectable viral load (< 40 copies.mL −1) ART: Inhibitor nucleoside analogue reverse transcriptase (NRTI): n = 49 (86.0%) Non-nucleoside reverse transcriptase inhibitor (NNRTI): n = 30 (52.6%) Protease Inhibitor (PI): n = 39 (68.4%) Disease stage: Stage 1 = 59.6% [34/57] Stage 2 = 35.1% [20/57]) Stage 3 = 5.3% [3/57]
da Silva et al.,[5] Santa Maria (RS), Brasil (2011)	Cross-sectional study	38 children and adolescents ♂: 16 ♀: 22	6 to 18 years	Viral charge: NR ART: Average duration 77 ± 41 months (range, 5.4-155.7 months; median, 76 months) Disease stage: NR

ART = antiretroviral therapy; SC = Santa Catarina; RS = Rio Grande do Sul; HIV = human immunodeficiency virus; CDC = Centers for Disease Control and Prevention; ♂: male sex; ♀: female sex; NR = not reported; *Information on authorship of this study.

Table 2. Objectives, assessment instruments and forms of classification of body image, statistical analyzes, and results found in studies on body image in children and adolescents diagnosed with human immunodeficiency virus (HIV) infection

Author/Year	Study objectives	Body image assessment instrument/Body image classification form	Statistical analysis	Results of prevalence of body image dissatisfaction	Results found Correlations and/or factors associated with body image dissatisfaction
"AIDS among children--United States, 1996.[16] Division of HIV/AIDS Prevention, CDC", New York, Florida, New Jersey, California, Puerto Rico and Texas - United States (1997)	Summarizing the Epidemiology of AIDS in Children in the United States reported from 1982 to 1996.	Dusek's short form of the Secord-Jourard Body Cathexis Scale (1983) Classification Body image: Answers one-two were classified as "I don't like my body," three were classified as "neutral," and four and five as "positive feelings"	Descriptive statistics Pearson correlation Multiple regression	NR	Dissatisfaction with body image was correlated with low self-esteem, low level of physical activity, and higher body fat when compared to the group satisfied with body image.
Alves Junior et al.,[3] 2021	Check for differences in body fat values assessed by different methods according to the perception of body image of HIV-infected children and adolescents.	Silhouette Scale previously validated with adolescents from Florianópolis (Adami et al.,[11] 2012). Body image classification: Satisfied (zero score); Want to reduce body weight (negative values); Want to increase body weight (positive values).	Covariance analysis	**Male** (P = 0.861 cohen-D = 0.579): Satisfied (n = 12/40.0%) Want to reduce body weight (n = 07/23.3%) Want to increase body weight (n = 11/36.7%) **Female** (P = 0.861 cohen-D = 0.579): Satisfied (n = 14/40.0%) Want to reduce body weight (n = 10/28.6%) Want to increase body weight (n = 11/31.4%)	**Male** There were no significant differences in body fat and body image indicators. **Female** Dissatisfaction with body image was associated with higher rates of trunk fat, total fat mass, and leg fat mass in relation to those satisfied with body image.
Augustemak de Lima et al.,[4] 2018	Verify possible associations of anthropometric indicators, infection/treatment, sexual maturity, and sociodemographic characteristics with body image in adolescents living with HIV.	Silhouette Scale previously validated with adolescents from Florianópolis (Adami et al.,[11] 2012) Body Image Classification: Satisfied; Want to reduce body weight; Want to increase body weight.	Chi-square test and Fisher's exact test Student's t test Mann-Whitney U Test Multiple linear regression	**Male (P = 0.009):** Satisfied (40.0%) Want to reduce body weight (8.0%) Want to increase body weight (52.0%) **Female (P = 0.285):** Satisfied (50.0%) Want to reduce body weight (21.9%) Want to increase body weight (28.1%)	Body image dissatisfaction was associated with female sex, older age, higher body weight, higher BMI, and greater arm muscle area in both sexes in relation to those satisfied with their body image.
da Silva et al.,[5] 2011	Check the prevalence of image satisfaction body of children and adolescents with HIV/AIDS, using HAART.	Silhouette scale validated by Kakeshita et al.[15] (2009) Body Image Classification: Satisfied with body image; Dissatisfied with thinness; Dissatisfied with being overweight.	Chi-square test Student's t test	**Total:** Satisfied with their body image (n = 6/15.8%) Dissatisfied with thinness (n = 16/42.1%) Dissatisfied with being overweight (n = 16/42.1%) **Male:** Satisfied with their body image (n = 03/18.8%) Dissatisfied with thinness (n = 08/50.0%) Dissatisfied with being overweight (n = 05/31.2%) **Female:** Satisfied with their body image (n = 03/13.6%) Dissatisfied with thinness (n = 08/36.4%) Dissatisfied with being overweight (n = 11/50.0%) **Children (age: NR):** Satisfied with their body image (n = 02/11.1%) Dissatisfied with thinness (n = 07/38.9%) Dissatisfied with overweight (n = 9/50.0%) **Adolescents (age: NR):** Satisfied with their body image (n = 04/20.0%) Dissatisfied with thinness (n = 09/45.0%) Dissatisfied with overweight (n = 07/35.0%)	Dissatisfaction with body image was associated with higher BMI and triceps skinfold in both sexes in relation to those satisfied with body image.

AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; BMI = body mass index; NR = not reported.

adolescents as "satisfied with their body image", "dissatisfied due to overweight", or "dissatisfied due to thinness"[5] (**Table 2**).

Regarding the results of articles found through this systematic review, it was found in three studies that children and adolescents of both sexes diagnosed with HIV infection were dissatisfied with their body image.[3-5] The prevalence of body image dissatisfaction due to thinness ranged from 36.7%[3] to 52.0%[4] for males and from 28.1%[4] to 36.4%[5] for females. The prevalence of body image dissatisfaction due to overweight ranged from 8.0%[4] to 31.2%[5] for males and from 21.9%[4] to 50.0%[5] for females (**Table 2**).

The factors associated with body image dissatisfaction found in this review were: low levels of physical activity, higher body fat and low self-esteem,[16] greater body weight, greater arm muscle area, greater triceps skinfold thickness [5], greater BMI,[4] and being older and female,[4] when compared to groups satisfied with their body image. Furthermore, body image dissatisfaction in females was associated with higher trunk fat, total fat mass, and leg fat mass in relation to those satisfied with their body image[3] (**Table 2**).

We found that of the four cross-sectional studies included in this review, one did not present clear information about the individuals that composed the population and sample, participation rate of eligible individuals, inclusion/exclusion criteria, justification for the sample size, and sampling power description or estimates of variance and effect, as well as a lack of previous measurement of the exposure variable and no detailed description of them.[16] Another study did not provide justification for the sample size, sample power description, or estimates of variance and effect, as well as a lack of previous measurement of the exposure variable.[5] The other studies (n = 2) did not evaluate the exposure variable before measuring the result or provide enough time to verify the effect of associations[3,4] (**Table 3**).

DISCUSSION

According to the full reading of the articles included in this systematic review,[3-5,16] children and adolescents diagnosed with HIV infection reported body image dissatisfaction due to both excess weight and thinness. The highest prevalence identified in both sexes was in relation to dissatisfaction due to thinness. In addition, factors associated with body image dissatisfaction were low levels of physical activity, higher body fat, and low self-esteem,[16] greater body weight, greater arm muscle area, greater triceps skinfold,[5] greater BMI,[4,5] in addition to being older and female.[4] Furthermore, body image dissatisfaction in females was associated with higher trunk fat, total fat mass, and leg fat mass.[3]

The fact that children and adolescents diagnosed with HIV infection of both sexes were dissatisfied due to thinness (they would like to increase their body weight) can be explained, in part, by the weight loss found in children and adolescents diagnosed with the infection. HIV infection has a direct effect on the inhibition of human growth hormone (hGH) synthesis.[20] Dissatisfaction due to thinness is recurrent mainly in male adolescents, due to the desire to have a stronger and more robust body.[4,21] However, in a study of this review, this type of dissatisfaction was more frequently reported by females.[4]

In addition, children and adolescents in this systematic review also showed dissatisfaction due to excess weight (would like to reduce body weight), but these prevalences were not higher than those reported in relation to dissatisfaction due to thinness. This can be explained by the negative effects of the mass media on body image perception, as body image dissatisfaction is strongly related to standards imposed by society and culture.[22,23] Thus, the increase in globalization and exposure to the ideal body (thin for females and muscular for males) through the media creates an even greater internal conflict in children and adolescentes.[23] The articles

Table 3. Assessment of methodological quality in cross-sectional studies on body image in children and adolescents diagnosed with human immunodeficiency virus (HIV) infection

Author(s), year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score Total
"AIDS among children-United States, 1996.[16] Division of HIV/AIDS Prevention, CDC", 1997	Y	N	NR	N	N	N	N	Y	Y	NA	Y	NA	NA	Y	08
Alves junior et al.,[3] 2021	Y	Y	Y	Y	Y	N	N	Y	Y	NA	Y	NA	NA	Y	12
Augustemak de Lima et al.,[4] 2018.	Y	Y	Y	Y	Y	N	N	Y	Y	NA	Y	NA	NA	Y	12
da Silva et al.,[5] 2011	Y	Y	NR	Y	N	N	N	Y	N	NA	Y	NA	NA	NA	09

Y = yes; N = no; NA = not applicable; NR = not reported. 1- Was the research question or objective in this article clearly stated? 2- Was the study population clearly specified and defined? 3- Was the participation rate of eligible people at least 50%? 4- Were all subjects selected or recruited from the same or similar populations (including the same time period)? Were the inclusion and exclusion criteria for participating in the study pre-specified and applied uniformly to all participants? 5- Was a justification for the sample size, description of power, or estimates of variation and effect provided? 6- For the analyzes in this document, were the exposures of interest measured before the result(s) were measured? 7- Was the time frame long enough to reasonably expect to see an association between exposure and outcome, if any? 8- For exposures that may vary in amount or level, did the study examine different exposure levels in relation to outcome (eg. exposure categories or exposure measured as a continuous variable)? 9- Were exposure measures (independent variables) clearly defined, valid, reliable, and consistently implemented in all study participants? 10- Have the exposure(s) been evaluated more than once over time? 11- Were the outcome measures (dependent variables) clearly defined, valid, reliable, and consistently implemented in all study participants? 12- Were the outcome assessors blinded to the exposure status of the participants? 13- Was the loss to follow-up after the start of the study 20% or less? 14- The main potential confounding variables were measured and statistically adjusted for their impact on the relationship between exposure(s) and outcome(s).

included showed that body image dissatisfaction in children and adolescents diagnosed with HIV infection can be explained by the visible manifestations of HIV and the adverse effects of the treatment, such as weight loss and reduced muscle mass.[3-5,16]

Although studies included in the present review reported body image dissatisfaction in both sexes, this dissatisfaction differs from children and adolescents without an HIV infection diagnosis.[22,24-25] While in the present systematic review, the highest prevalence of body image dissatisfaction reported was due to thinness, the literature shows that in female children and adolescents without HIV infection diagnosis, body image dissatisfaction is more recurrent due to overweight.[22,24-25] Females in general want to reduce their body silhouette[22,24-25] and not increase it, as verified in this systematic review for females with HIV infection diagnosis. This difference in relation to results can be explained by the stigma related to HIV infection and the continuous use of medication.[20] These studies,[22,24-25] used the silhouette scales validated by Adami et al.[17] and the silhouette scale proposed by Kakeshita et al.[19] to assess body image, as well as studies included in the present systematic review.

Regarding associated factors, disorders related to body image are associated with low self-esteem and changes in body composition, which can be explained because children and adolescents with high body mass have difficulties in relation to self-acceptance, consequently reporting low self-esteem.[3-5,16] In addition, changes that occur during the transition period between childhood and adolescence, such as increase in body fat in the premenarche period, can generate body image dissatisfaction in females;[22,23] anthropometric and body composition changes are observed by the marked development of lean body mass and muscle mass, which are factors that can generate body image dissatisfaction in males.[25,26]

In relation to associated factors, the loss of a child's role and identity in both sexes can generate body image dissatisfaction.[25,26] In an analysis of body image dissatisfaction in several European countries with children and adolescents without a diagnosis of HIV infection, it was reported that high BMI values were associated with body image dissatisfaction.[26] On the other hand, studies with children and adolescents without diagnosis of HIV infection and with adequate BMI reported body image dissatisfaction.[28-29]

Of the studies included in the present systematic review, only one verified the presence of lipodystrophy and its association with body image;[5] however, it did not identify significant association for the sample. This can be explained by the assumption that infected individuals follow the same pattern of body image dissatisfaction as healthy individuals in the age group evaluated.[5] In addition, although changes in body fat are noticeable to the evaluating physician, in children and adolescents, such changes are not as evident as in adults; this may not be perceived as a generator of body image dissatisfaction in children and adolescents with an HIV diagnosis.[5] However, it is noteworthy that this study, considered a pioneer in Brazil in the assessment of body image in children and adolescents diagnosed with HIV infection using antiretroviral therapy, has limitations, such as lack of a control group, sample size, and time of data collection, which can impact the results.[5] In the long term, adult individuals diagnosed with HIV infection have high levels of body image dissatisfaction, resulting in worse quality of affective and social relationships with friends and family.

The different protocols found in this review can be explained by the gradual increase in scientific production related to body image and the need for adequate instruments to assess certain age groups (children, adolescents, adults, and older adults).[30] All studies included in this systematic review used assessment methods validated for use in children and adolescents in general. This systematic review showed that there are no specific validated instruments to assess body image of children and adolescents diagnosed with HIV infection, which opens an opportunity for further studies. Furthermore, the use of silhouette scales[17,19] and others such as the Dusek's Secord-Jourard Body Cathexis Scale[18] to measure body image is recurrent among researchers who investigate body image and body dissatisfaction in children and adolescentes.[17] Assessments using full-body silhouette scales[17,19] and body regions and functions scales[31] are related to the attitudinal component, that is, they aim to measure the individuals' ability to perceive their own body dimension.[32] The methods used to assess body image consider that the body image perception is not a mere challenge to see well, but to capture and interpret what is seen according to the body identity of each individual.[19] However, the different instruments used to assess body image make further comparisons between studies difficult.[30]

It is important to mention the fact that of studies included in the present review, one carried out in the United States[7] and the others in southern Brazil.[3-5] The cultural differences of each country can influence the results obtained in each study.[33] It is inevitable that each individual internalizes a set of beliefs, attitudes, values, and behaviors, which are transmitted from generation to generation and common to all individuals in a given culture.[34]

Regarding the results of the assessment of the risk of bias/methodological quality of studies, it was possible to identify that two studies reached a score of 12,[3,4] one study 9[5] and one 8.[16] All had scores considered to be of moderate risk of bias/reasonable methodological quality.[12] This means that studies are susceptible to some bias errors, but such errors are considered insufficient to invalidate the results.[15] As a characteristic of studies with reasonable methodological quality, variation was identified in relation to strengths and limitations.[15] The assessment of the risk of bias/methodological quality of studies is a tool that helps reviewers to focus on concepts that are fundamental to the internal validity of each study.[15]

Among the limitations of this review, the cross-sectional design of all included studies should be highlighted, which does not allow temporal or causal relationships. Furthermore, due to the small

number of studies, it was not possible to carry out more in-depth analyses regarding the differences between sexes and age groups, and the different instruments used to assess body image make the comparison of results difficult. Another limitation identified by the review was the fact that there is a nearly four decades of difference between the United States study, which reported cumulative data from 1982 to 1996,[16] and the other three studies included in the present review.[3-5] This time difference between studies makes it difficult to generalize the findings because, over four decades, cultural characteristics and the body perception and relationship may change as a result of the dynamics of society. Furthermore, HIV treatment has made significant advances that have improved patients' quality of life over these four decades.

As positive aspects of this study, the pioneering of conducting a systematic review of body image in children and adolescents diagnosed with HIV infection stands out, adopting a search strategy in eight different databases. Lastly, it is suggested for future studies that the presence of children and adolescents with acquired immunodeficiency syndrome (AIDS) and not only those diagnosed with HIV infection be identified in samples to better understand the influence of AIDS on body image and associated factors.

CONCLUSIONS

In conclusion, the findings of this systematic review show that children and adolescents of both sexes diagnosed with HIV infection are dissatisfied with their body image. Regarding factors associated with body image, low levels of physical activity, greater body fat, low self-esteem, greater body weight, greater arm muscle area, greater triceps skinfold, and greater BMI were identified in both sexes and are associated with body image dissatisfaction. There is no consensus on how body image is assessed, given the variety of instruments identified in this review, which demonstrates the need for monitoring and developing interventions aimed at reducing body image dissatisfaction.

REFERENCES

1. Alam N, Cortina-Borja M, Goetghebuer T, et al. Body fat abnormality in HIV-infected children and adolescents living in Europe: prevalence and risk factors. J Acquir Immune Defic Syndr. 2012;59(3):314-24. PMID: 22205436; https://doi.org/10.1097/QAI.0b013e31824330cb.
2. Alencastro PR, Barcellos NT, Wolff FH, et al. People living with HIV on ART have accurate perception of lipodystrophy signs: a cross-sectional study. BMC Res Notes. 2017;10(1):40. PMID: 28086977; https://doi.org/10.1186/s13104-017-2377-3.
3. Alves Junior CAS, Martins PC, de Andrade Gonçalves EC, et al. Association between body fat distribution assessed by different techniques and body image perception in HIV-infected children and adolescents. J Pediatr Nurs. 2021;60:e74-e79. PMID: 33846040; https://doi.org/10.1016/j.pedn.2021.03.025.
4. Augustemak de Lima LR, Monteiro Teixeira D, Custódio Martins P, et al. Body image and anthropometric indicators in adolescents living with HIV. Rev Bras Cineantropom Hum. 2018;20(1):53-63. https://doi.org/10.5007/1980-0037.2018v20n1p53.
5. da Silva QH, Pedro FL, Kirsten VR. Body satisfaction and lipodystrophy characteristics in HIV/AIDS children and teenagers undergoing highly active antiretroviral therapy. Rev Paul Pediatr. 2011;29(3):357-63. https://doi.org/10.1590/S0103-05822011000300009.
6. Soares LR, Casseb JSDR, Chaba DCDS, et al. Self-reported lipodystrophy, nutritional, lipemic profile and its impact on the body image of HIV-1-infected persons, with and without antiretroviral therapy. AIDS Care. 2020;32(10):1317-22. PMID: 31711307; https://doi.org/10.1080/09540121.2019.1687832.
7. Fisher S. A evolução dos conceitos psicológicos sobre o corpo. In: Cash TF, Pruzinsky T, editors. Body images: Development, deviance, and change. New York: Guilford Press; 1990. p. 3-20.
8. Gardner RM. What affects body size estimation? The role of eating disorder, obesity, weight loss, hunger, restrained eating, mood, depression, sexual abuse, menstrual cycle, media influence and gender. Current Psychiatry Reviews. 2011;7(2):96-103. https://doi.org/10.2174/157340011796391193.
9. Neves AN, Morgado FFR, Tavares MCGCF. Avaliação da Imagem Corporal: Notas Essenciais para uma Boa Prática de Pesquisa. Psic: Teor Pesq. 2015;31(3):375-80. https://doi.org/10.1590/0102-37722015031945375380.
10. De-la-Torre-Ugarte-Guanilo MC, Takahashi RF, Bertolozzi MR. Revisão sistemática: noções gerais [Systematic review: general notions]. Rev Esc Enferm USP. 2011;45(5):1260-6. PMID: 22031392; https://doi.org/10.1590/S0080-2342011000500033.
11. Campos Matos A, Scotto Boletini R, Keating TC, Fumie Matsumoto N, Gandolpho M. Tratamento da lipoatrofia facial em pessoas vivendo com HIV/AIDS: afastando o preconceito e melhorando a qualidade de vida. O Mundo da Saúde. 2010;34(2):210-7. https://doi.org/10.15343/0104-7809.20102210217.
12. O'Dea RE, Lagisz M, Jennions MD, et al. Preferred reporting items for systematic reviews and meta-analyses in ecology and evolutionary biology: a PRISMA extension. Biol Rev Camb Philos Soc. 2021;96(5):1695-722. PMID: 33960637; https://doi.org/10.1111/brv.12721.
13. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142. PMID: 31643080; https://doi.org/10.1002/14651858.ED000142.
14. Pellizzon RF. Pesquisa na área da saúde: 1. Base de dados DeCS (Descritores em Ciências da Saúde). Acta Cir Bras. 2004;19(2):153-63. https://doi.org/10.1590/S0102-86502004000200013.
15. NHLBI: National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies [Internet]. Bethesda: National Institutes of Health, Department of Health and Human Services; 2016 Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed in 2022 (Jun 3).
16. AIDS among children--United States, 1996. Division of HIV/AIDS Prevention, CDC. J Sch Health. 1997;67(4):141-3. PMID: 9130192; https://doi.org/10.1111/j.1746-1561.1997.tb03434.x.

17. Adami F, Schlickmann Frainer DE, de Souza Almeida F, et al. Construct validity of a figure rating scale for Brazilian adolescents. Nutr J. 2012;11:24. PMID: 22500605; https://doi.org/10.1186/1475-2891-11-24.
18. Dusek DE. Thin and Fit: Your personal lifestyle. Belmont, CA: Wadsworth Publishing Co.; 1982.
19. Kakeshita IS, Silva AIP, Zanatta DP, Almeida SS. Construção e fidedignidade teste-reteste de escalas de silhuetas brasileiras para adultos e crianças. Psic: Teor e Pesq. 2009;25(2):263-70. https://doi.org/10.1590/S0102-37722009000200015.
20. Chantry CJ, Cervia JS, Hughes MD, et al. Predictors of growth and body composition in HIV-infected children beginning or changing antiretroviral therapy. HIV Med. 2010;11(9):573-83. PMID: 20345880; https://doi.org/10.1111/j.1468-1293.2010.00823.x.
21. Silva AF, Moraes MS, Martins PC, et al. Prevalence of body image dissatisfaction and association with teasing behaviors and body weight control in adolescents. Motriz: Rev Educ Fis. 2020;26(1):e10200198. https://doi.org/10.1590/s1980-6574202000010198.
22. Chapman E. Body image issues among individuals with HIV and AIDS. In: Cash TF, Pruzinski T, editors. Body image: a handbook of theory, research, and clinical practice. New York: The Guilford Press; 2002. p. 395-402.
23. Anderson-Fye EP. Cultural influences on body image and eating disorders. In: Agras WS, Robinson A, editors. The Oxford Handbook of Eating Disorders. United Kingdom: Oxford University Press; 2018. p: 187-208. https://doi.org/10.1093/oxfordhb/9780190620998.013.9.
24. Petroski EL, Pelegrini A, Glaner MF. Motivos e prevalência de insatisfação com a imagem corporal em adolescentes [Reasons and prevalence of body image dissatisfaction in adolescents]. Cien Saude Colet. 2012;17(4):1071-7. PMID: 22534860; https://doi.org/10.1590/S1413-81232012000400028.
25. Braggion GF, Matsudo VKR, Matsudo SMM. Consumo alimentar, atividade física e percepção da aparência corporal em adolescentes. Rev Bras Ciênc Mov. 2000;8(1):15-22. https://doi.org/10.18511/rbcm.v8i1.350.
26. Borges FS, Matsudo SM, Matsudo VK. Perfil antropométrico e metabólico de rapazes pubertários da mesma idade cronológica em diferentes níveis de maturação sexual. Rev Bras Ciênc Mov. 2004;12(4):7-12. https://doi.org/10.18511/rbcm.v12i4.579.
27. Bauer M, Kirchengast S. Body composition, weight status, body image and weight control practices among female adolescents from eastern Austria. Anthropol Anz. 2006;64(3):321-31. PMID: 17128935.
28. Marques MI, Pimenta J, Reis S, et al. (In)Satisfação com a imagem corporal na adolescência. Rev Nascer e Crescer. 2016;25(4):217-21. Available from: https://repositorio.chporto.pt/handle/10400.16/2029. Accessed in 2022 (Jun 3).
29. Petroski EL, Pelegrini A, Glaner MF. Insatisfação corporal em adolescentes rurais e urbanos. Motricidade. 2009;5(4):13-25. Available from: https://www.revistamotricidade.com/arquivo/2009_vol5_n4/v5n4a03.pdf. Accessed in 2022 (Jun 3).
30. Rocha Morgado FF, Caputo Ferreira ME, Maia Andrade MR, Josiany Segheto K. Análise dos instrumentos de avaliação da imagem corporal. Fitness & Performance Journal. 2009;8(3):204-11. Available from: https://www.redalyc.org/pdf/751/75112567007.pdf. Accessed in 2022 (Sep 15).
31. Dusek DE. Thin and Fit: Your personal lifestyle. Belmont, CA: Publishing Co.; 1983.
32. Thurm BE, Miranda MLJ, Salzano FT, et al. Revisão dos métodos empregados na avaliação da dimensão corporal em pacientes com transtornos alimentares. J Bras Psiquiatr. 2011;60(4):331-6. https://doi.org/10.1590/S0047-20852011000400015.
33. Braga PD, Molina Mdel CB, de Figueiredo TA. Representações do corpo: com a palavra um grupo de adolescentes de classes populares [Representations of the body: with the word one group of adolescents from popular classes]. Cien Saude Colet. 2010;15(1):87-95. PMID: 20169235; https://doi.org/10.1590/S1413-81232010000100014.
34. Alves D, Pinto M, Alves S, Mota A, Leirós V. Cultura e imagem corporal. Motricidade. 2009;5(1):1-20. Available from: https://www.researchgate.net/publication/262670612_Cultura_e_imagem_corporal. Accessed in 2022 (Jun 3).

Authors' contributions: Zanlorenci S: systematic search, full reading of the articles inserted, choice of articles included in the review, writing of the manuscript as a whole; da Silva AF: systematic search, full reading of the articles inserted, choice of articles included in the review, writing of the manuscript as a whole; and Silva DAS: systematic search, full reading of the articles inserted, choice of articles included in the review, writing of the manuscript as a whole, review of the manuscript. All authors actively contributed to the discussion of study results and all reviewed and approved the final version to be published

Sources of funding: There are no funding sources
Conflicts of interest: There are no conflicts of interest

Date of first submission: March 17, 2022
Last received: July 24, 2022
Accepted: August 19, 2022

Address for correspondence:
Diego Augusto Santos Silva
Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC)
R. Eng. Agronômico Andrei Cristian Ferreira, s/nº
Trindade, Florianópolis (SC) — Brasil
CEP 88040-900
Tel. (+55 48) 3721-6342
E-mail: diegoaugustoss@yahoo.com.br

Appendix 1. Keywords

1 - PubMed via National Library of Medicine (MEDLINE) search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***All fields:*** 52,279 ***Title/abstract:*** 42,425
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***All fields:*** 29,294 ***Title/abstract:*** 15,491
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"*	***All fields:*** 671 ***Title/abstract:*** 380
(("*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*") AND (*child** OR *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR "*young people*" OR "*school children*" OR "*school teenager*" OR *young* OR *childhood* OR "*children with HIV*" OR "*adolescents with HIV*" OR "*children infected with HIV*" OR "*adolescents infected with HIV*" OR "*HIV children*" OR "*HIV adolescents*" OR "*children living with HIV*" OR "*adolescents living with HIV*")) AND (HIV OR AIDS OR "*Human Immunodeficiency Virus*" OR "*Acquired Immunodeficiency Syndrome*") *Filters applied: Female, Male, Child: birth-18 years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years*		405

2 - Web of Science search performed on: October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***All fields:*** 76,697 ***Title:*** 20,625
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***All fields:*** 38,708 ***Title:*** 6,041
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"*	***All fields:*** 907 ***Title:*** 24
You searched for: ALL FIELDS: ("body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception") AND ALL FIELDS: (*child** OR *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR "*young people*" OR "*school children*" OR "*school teenager*" OR *young* OR *childhood* OR "*children with HIV*" OR "*adolescents with HIV*" OR "*children infected with HIV*" OR "*adolescents infected with HIV*" OR "*HIV children*"		465

3 - Scopus search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***All fields:*** 183,568 ***Title/abstract/keywords:*** 11,456
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***All fields:*** 831 ***Title/abstract/keywords:*** 1
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"*	***All fields:*** 419 ***Title/abstract/keywords:*** 0
(ALL ("*body* AND *image*" OR "*self* AND *perception*" OR "*self* AND *image*" OR "*body* AND *satisfaction*" OR "*body* AND *dissatisfaction*" OR "*self* AND *esteem*" OR "*body* AND *perception*" OR "*weight* AND *perception*") AND ALL (*child** O R *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *t eenage* OR *teenager* OR *scholar* OR "*young* AND *people*" OR "*school* AND *child ren*" OR "*school* AND *teenager*" OR *young* OR *childhood* OR "*children* AND *wit h* AND *hiv*" OR "*adolescents* AND *with* AND *hiv*" OR "*children* AND *infected* A ND *with* AND *hiv*" OR "*adolescents* AND *infected* AND *with* AND *hiv*" OR "*hiv* AND *children*" OR "*hiv* AND *adolescents*" OR "*children* AND *living* AND *with* A ND *hiv*" OR "*adolescents* AND *living* AND *with* AND *hiv*") AND ALL (*hiv* OR *aids* OR "*human* AND *immunodeficiency* AND *virus*" OR "*acquired* AND *immuno deficiency* AND *syndrome*")) AND (EXCLUDE (SUBJAREA, "BIOC") OR EX CLUDE (SUBJAREA, "IMMU") OR EXCLUDE (SUBJAREA, "ARTS") OR E XCLUDE (SUBJAREA, "AGRI") OR EXCLUDE (SUBJAREA , "DENT") OR EXCLUDE (SUBJAREA, "PHAR") OR EXCLUDE (SUBJAREA, "ENGI") OR EXCLUDE (SUBJAREA, "ENVI") OR EXCLUDE (SUBJAREA, "CENG") OR EXCLUDE (SUBJAREA, "BUSI") OR EXCLUDE (SUBJAREA, "EART") OR EXCLUDE (SUBJAREA, "ECON") OR EXCLUDE (SUBJAREA, "VETE") OR EXCLUDE (SUBJAREA, "CHEM") OR EXCLUDE (SUBJAREA, "COMP") O R EXCLUDE (SUBJAREA, "MATH"))		286

Continue...

Appendix 1. Continuation.

4 - SPORTDiscus via EBSCOhost search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***Full text:*** 38,567 ***Title:*** 2,905 ***Abstract:*** 6,665
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***Full text:*** 30,515 ***Title:*** 886 ***Abstract:*** 2,998
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"*	***Full text:*** 3.075 ***Title:*** 02 ***Abstract:*** 18
TX ("*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*") AND TX (*child** OR *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR "*young people*" OR "*school children*" OR "*school teenager*" OR *young* OR *childhood* OR "*children with HIV*" OR "*adolescents with HIV*" OR "*children infected with HIV*" OR "*adolescents infected with HIV*" OR "*HIV children*" OR "*HIV adolescents*" OR "*children living with HIV*" OR "*adolescents living with HIV*") AND TX (HIV OR AIDS OR "*Human Immunodeficiency Virus*" OR "*Acquired Immunodeficiency Syndrome*") Restringir por *SubjectThesaurus: psychology, psychological stress, health, health behavior, physical education, quality of life, attitude (psychology), public health, self-perception, mental depression, physical activity, mental health, college students, physical fitness, medical care, health promotion, risk-taking behavior, therapeutics, hiv infections, motivation (psychology), exercise, self-evaluation, self-efficacy, teenagers, psychological tests, body image, hiv-positive persons, sports, well-being, emotions, sports psychology, anxiety, athletes, health education, hiv, self-esteem, patients, eating disorders, education, personality, aids, nutrition, diseases, distress (psychology), universities & colleges, health status indicators, decision making, adolescent psychology, body mass index, perception, health attitudes, cognition, leisure, sexually transmitted dise..., women, mental illness, social psychology, teenagers' health, women's health, disease risk factors, obesity, youth, motor ability, psychology of college stu..., treatment effectiveness, children, college athletes, diet, physiology, resilience (personality t..., child development, chronic diseases, dietary supplements, gender identity, human sexuality, prevention, medical personnel, body weight, pathological psychology, lifestyles, undergraduates, aids patients, intention, physical education teache..., physical training & condi..., sports participation, educational attainment, evidence-based medicine, life skills, school children, weight loss, young adults, body composition, children's health, diagnosis, ethics, high school students, medical screening, recreation, food habits, psychology of women, sports sciences, stress management, student attitudes, exercise therapy, recreational therapy, sex education, sports personnel, students, symptoms, child psychology, childhood obesity, cognitive therapy, college student attitudes, goal (psychology), health self-care, regulation of body weight, teachers* *sports psychology, anxiety, athletes, health education, hiv, self-esteem, patients, eating disorders, education, personality, aids, nutrition, diseases, distress (psychology), universities & colleges, health status indicators, decision making, adolescent psychology, body mass index, perception, health attitudes, cognition, leisure, sexually transmitted dise..., women, mental illness, social psychology, teenagers' health, women's health, disease risk factors, obesity, youth, motor ability, psychology of college stu..., treatment effectiveness, children, college athletes, diet, physiology, resilience (personality t..., child development, chronic diseases, dietary supplements, gender identity, human sexuality, prevention, medical personnel, body weight, pathological psychology, lifestyles, undergraduates, aids patients, intention, physical education teache..., physical training & condi..., sports participation, educational attainment, evidence-based medicine, life skills, school children, weight loss, young adults, body composition, children's health, diagnosis, ethics, high school students, medical screening, recreation, food habits, psychology of women, sports sciences, stress management, student attitudes, exercise therapy, recreational therapy, sex education, sports personnel, students, symptoms, child psychology, childhood obesity, cognitive therapy, college student attitudes, goal (psychology), health self-care, regulation of body weight, teachers*	507

Continue...

Appendix 1. Continuation.

5 - LILACS via Biblioteca Virtual em Saúde search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*body image* OR *self perception* OR *self image* OR *body satisfaction* OR *body dissatisfaction* OR *self esteem* OR *body perception* OR *weight perception*	***Words:*** 2,567 ***Title:*** 00 ***Abstract:*** 00
1 + 2	*child$* OR *adolec$* OR *student* OR *youth* OR *adolescent$* OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR *young people* OR *school children* OR *school teenager* OR *young* OR *childhood* OR *children with HIV* OR *adolescents with HIV* OR *children infected with HIV* OR *adolescents infected with HIV* OR *HIV children* OR *HIV adolescents* OR *children living with HIV* OR *adolescents living with HIV*	***Words:*** 00 ***Title:*** 00 ***Abstract:*** 00
1 + 2 + 3	HIV OR AIDS OR *Human Immunodeficiency Virus* OR *Acquired Immunodeficiency Syndrome*	***Words:*** 21 ***Title:*** 00 ***Abstract:*** 0
body image OR *self perception* OR *self image* OR *body satisfaction* OR *body dissatisfaction* OR *self esteem* OR *body perception* OR *weight perception* [*words*] and *child$* OR *adolec$* OR *student* OR *youth* OR *adolescent$* OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR *young people* OR *school children* OR *school teenager* OR *young* OR *childhood* OR *children with HIV* OR *adolescents with HIV* OR *children infected with HIV* OR *adolescents infected with HIV* OR *HIV children* OR *HIV adolescents* OR *children living with HIV* OR *adolescents living with HIV* [*words*] and HIV OR AIDS OR *Human Immunodeficiency Virus* OR *Acquired Immunodeficiency Syndrome* [*words*]	21	
1	*Imagen corporal OR autopercepción OR autoimagen OR satisfacción corporal OR insatisfacción corporal OR autoestima OR percepción corporal OR percepción del peso*	***Words:*** 4,306 ***Title:*** 462 ***Abstract:*** 2,134
1 + 2	*niño$ OR adolescente$ OR estudiante OR joven OR adolescencia OR escolar OR jóvenes OR niños en edad escolar OR adolescente en edad escolar OR joven OR niñez OR niños con VIH OR adolescentes con VIH OR niños infectados con el VIH OR adolescentes infectados con el VIH OR niños con VIH OR adolescentes con VIH OR niños que viven con el VIH OR adolescentes que viven con el VIH*	***Words:*** 1,823 ***Title:*** 104 ***Abstract:*** 621
1 + 2 + 3	*VIH OR SIDA OR Virus de inmunodeficiencia humana OR Síndrome de inmunodeficiencia adquirida*	***Words:*** 35 ***Title:*** 00 ***Abstract:*** 11
Imagen corporal OR *autopercepción* OR *autoimagen* OR *satisfacción corporal* OR *insatisfacción corporal* OR *autoestima* OR *percepción corporal* OR *percepción del peso* [*Words*] AND *niño$* OR *adolescente$* OR *estudiante* OR *joven* OR *adolescencia* OR *escolar* OR *jóvenes* OR *niños en edad escolar* OR *adolescente en edad escolar* OR *joven* OR *niñez* OR *niños con VIH* OR *adolescentes con VIH* OR *niños infectados con el VIH* OR *adolescentes infectados con el VIH* OR *niños con VIH* OR *adolescentes con VIH* OR *niños que viven con el VIH* OR *adolescentes que viven con el VIH* [*Words*] AND VIH OR SIDA OR *Virus de inmunodeficiencia humana* OR *Síndrome de inmunodeficiencia adquirida* [*Words*]	35	

Continue...

Appendix 1. Continuation.

6 - Scientific Eletronic Library Online (SciELO) search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	"*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*"	***All fields:*** 961 ***Abstract:*** 821 ***Title:*** 131
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***All fields:*** 00 ***Title:*** 00 ***Abstract:*** 00
1 + 2 + 3	HIV OR AIDS OR "*Human Immunodeficiency Virus*" OR "*Acquired Immunodeficiency Syndrome*"	***All fields:*** 00 ***Title:*** 00 ***Abstract:*** 00
("*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*") AND (*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV") AND (*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome")	00	
1	*"Imagen corporal" OR "autopercepción" OR "autoimagen" OR "satisfacción corporal" OR "insatisfacción corporal" OR "autoestima" OR "percepción corporal" OR "percepción del peso"*	***Todos los índices:*** 2,228 ***Resumen:*** 2,011 ***Título:*** 585
1 + 2	*niño* OR adolescente* OR estudiante OR joven OR adolescencia OR escolar OR jóvenes OR "niños en edad escolar" OR "adolescente en edad escolar" OR joven OR niñez OR "niños con VIH" OR "adolescentes con VIH" OR "niños infectados con el VIH" OR "adolescentes infectados con el VIH" OR "niños con VIH" OR "adolescentes con VIH" OR "niños que viven con el VIH" OR "adolescentes que viven con el VIH"*	***Todos los índices:*** 00 ***Resumen:*** 00 ***Título:*** 00
1 + 2 + 3	VIH OR SIDA OR "*Virus de inmunodeficiencia humana*" OR "*Síndrome de inmunodeficiencia adquirida*"	***Todos los índices:*** 00 ***Resumen:*** 00 ***Título:*** 00
("*Imagen corporal*" OR "*autopercepción*" OR "*autoimagen*" OR "*satisfacción corporal*" OR "*insatisfacción corporal*" OR "*autoestima*" OR "*percepción corporal*" OR "*percepción del peso*") AND (*niño** OR *adolescente** OR *estudiante* OR *joven* OR *adolescencia* OR *escolar* OR *jóvenes* OR "*niños en edad escolar*" OR "*adolescente en edad escolar*" OR *joven* OR *niñez* OR "*niños con VIH*" OR "*adolescentes con VIH*" OR "*niños infectados con el VIH*" OR "*adolescentes infectados con el VIH*" OR "*niños con VIH*" OR "*adolescentes con VIH*" OR "*niños que viven con el VIH*" OR "*adolescentes que viven con el VIH*") AND (VIH OR SIDA OR "*Virus de inmunodeficiencia humana*" OR "*Síndrome de inmunodeficiencia adquirida*")	00	

7 - PsycINFO via American Psychological Association (APA) search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***All fields:*** 103,817 ***Title:*** 21,034 ***Abstract:*** 63,778
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***All fields:*** 58,888 ***Title:*** 5,062 ***Abstract:*** 24,447
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"*	***All fields:*** 986 ***Title:*** 20 ***Abstract:*** 342
"*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*" *AND* ***Any Field:*** *child** OR *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR "*young people*" OR "*school children*" OR "*school teenager*" OR *young* OR *childhood* OR "*children with HIV*" OR "*adolescents with HIV*" OR "*children infected with HIV*" OR "*adolescents infected with HIV*" OR "*HIV children*" OR "*HIV adolescents*" OR "*children living with HIV*" OR "*adolescents living with HIV*" *AND* ***Any Field:*** HIV OR AIDS OR "*Human Immunodeficiency Virus*" OR "*Acquired Immunodeficiency Syndrome*" *AND* ***Publication Type:*** *Peer Reviewed Journal AND* ***Age Group:*** *Adolescence (13-17 yrs) AND* ***Age Group:*** *Childhood (birth-12 yrs) AND* ***Age Group:*** *School Age (6-12 yrs) AND* ***Age Group:*** *Preschool Age (2-5 yrs)*	08	

Continue...

Appendix 1. Continuation.

8 - Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost search performed on October 6, 2021.		
Bloc	**Descriptors**	**Articles**
1	*"body image" OR "self perception" OR "self image" OR "body satisfaction" OR "body dissatisfaction" OR "self esteem" OR "body perception" OR "weight perception"*	***Full texts:*** 66,194 ***Title:*** 7,224 ***Abstract:*** 21,517
1 + 2	*child* OR adolec* OR student OR youth OR adolescent* OR adolescence OR teen OR teenage OR teenager OR scholar OR "young people" OR "school children" OR "school teenager" OR young OR childhood OR "children with HIV" OR "adolescents with HIV" OR "children infected with HIV" OR "adolescents infected with HIV" OR "HIV children" OR "HIV adolescents" OR "children living with HIV" OR "adolescents living with HIV"*	***Full texts:*** 47,812 ***Title:*** 2,285 ***Abstract:*** 9,056
1 + 2 + 3	*HIV OR AIDS OR "Human Immunodeficiency Virus" OR "Acquired Immunodeficiency Syndrome"* TX ("*body image*" OR "*self perception*" OR "*self image*" OR "*body satisfaction*" OR "*body dissatisfaction*" OR "*self esteem*" OR "*body perception*" OR "*weight perception*") AND TX (*child** OR *adolec** OR *student* OR *youth* OR *adolescent** OR *adolescence* OR *teen* OR *teenage* OR *teenager* OR *scholar* OR "*young people*" OR "*school children*" OR "*school teenager*" OR *young* OR *childhood* OR "*children with HIV*" OR "*adolescents with HIV*" OR "*children infected with HIV*" OR "*adolescents infected with HIV*" OR "*HIV children*" OR "*HIV adolescents*" OR "*children living with HIV*" OR "*adolescents living with HIV*") AND TX (HIV OR AIDS OR "*Human Immunodeficiency Virus*" OR "*Acquired Immunodeficiency Syndrome*") ***Restringir por SubjectAge:*** *- all infant, child: 6-12 years, adolescent: 13-18 years, all child, child, preschool: 2-5 years.* ***Restringir por SubjectMajor:*** *hiv infections, sexuality, quality of life, hiv- positive persons, risk taking behavior, stigma, support, psychosocial, black persons, depression, health behavior, self concept, women, adaptation, psychological, stress, psychological, women's health, health promotion, mental health, chronic disease, students, college, mental disorders, interpersonal relations, psychological well-being, life experiences, patient attitudes, sex education, acquired immunodeficiency..., gay men, adolescent behavior, health services accessibi..., health status, communication, attitude to sexuality, attitude to health, self care, hispanic americans, body image, sexually transmitted dise..., palliative care, sexual health, parent-child relations, coping, hardiness, adolescent health, caregivers, health knowledge, decision making, homosexuality, truth disclosure, attitude to aids, lgbtq+ persons, perception, health education, self-efficacy, students, high school, adolescent psychology, student attitudes, students, attitude, family relations, anxiety, hiv seropositivity, motivation, pediatric obesity, counseling, disease transmission*	***Full texts:*** 7,016 ***Title:*** 19 ***Abstract:*** 209

Moonlighting and physician residents' compensation: is it all about money? A cross-sectional Brazilian study

Mário Luciano de Mélo Silva-Júnior[I], Pedro Augusto Sampaio Rocha-Filho[II]

Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil

[I]MD, PhD. Professor, Medical School, Division of Neuropsychiatry, Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil; Professor, Neurology Unit, Medical School, Uninassau, Recife (PE), Brazil; Physician, Neurology Unit, Hospital da Restauração, Recife (PE), Brazil.
https://orcid.org/0000-0002-9002-107X

[II]MD, PhD. Professor, Medical School, Division of Neuropsychiatry, Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil. Professor, Postgraduate Program in Neuropsychiatry and Behavioral Sciences (Posneuro), Universidade Federal do Pernambuco (UFPE), Recife (PE), Brazil; and Physician, Headache Clinic, Hospital Universitario Oswaldo Cruz, Universidade do Pernambuco (UPE), Recife (PE), Brazil.
https://orcid.org/0000-0001-5725-2637

KEYWORDS (MeSH terms):
Workload.
Internship and residency.
Remuneration.

AUTHORS' KEYWORDS:
Moonlighting.
Duty hours.
Medical residency.
Effort-reward imbalance.

ABSTRACT

BACKGROUND: Moonlighting is a largely discussed, however under-explored, subject among physician residents.

OBJECTIVES: To analyze the frequency of moonlighting and its related factors.

DESIGN AND SETTING: This cross-sectional study enrolled medical residents from all geographical regions of Brazil.

METHODS: A web-based structured closed-ended survey was applied that explored the frequency and type of moonlighting, residency programs characteristics, and psychological distress. The questionnaire was published on social networks.

RESULTS: The completion rate was 71.4% (n = 1,419) and 37.7% were males aged 28.8 ± 3.2 (mean ± standard deviation) years, and 571 (40.2%) were post-graduate year (PGY) 1. There were residents from 50 medical specialties (the most common training area was clinical, 51.9%). A total of 80.6% practiced moonlighting, with an average weekly workload of 14.1 ± 9.4 h, usually overnight or in weekend shifts. Factors related to it were being PGY-2 or higher (adjusted odds ratio = 3.90 [95% confidence interval = 2.93–5.18], logistic regression), lower weekly residency duty hours (0.98 [0.97–0.99]), and a higher salary (1.23 [1.08–1.40]). In contrast, perception of a "fair/adequate" compensation was influenced by age (1.02 [1.01–1.02]), not being single (1.05 [1.01–1.10]), and residency duty hours (1.51 [1.22–1.88]). Depression, anxiety, diurnal somnolence scores, and work-personal life conflicts were not correlated with moonlighting status.

CONCLUSION: Moonlighting frequency is high, and it is related to higher PGY, briefer residency duty hours, and the perception that remuneration should be higher. This study provides insights into the motivations for moonlighting and effort-reward imbalance.

INTRODUCTION

In the case of physician residents, moonlighting refers to medical practice unrelated to training requisites. Residents have perceived positive effects of moonlighting, such as gain of autonomy, experience, and competence;[1] however, the main motivation to do so seems to be financial.[2,3]

In Brazil, medical residency programs pay a remuneration of approximately R$ 36,000 per year (Brazilian currency, equivalent to 8,490 US dollars, considering the exchange during the period of our data collection, in 2019), and the residents should work 60 hours per week. This compensation is lower than that practiced in other South American countries, such as Colombia and Peru.[4,5] For comparison purposes, the mean salary of an attending physician in Brazil is estimated to be R$ 229,500 (54,127 US dollars) per year, with a mean workload of 55 hours per week.[6] Residents' low remuneration, associated with living costs in large cities, the need to support family members, and debts from medical college, leads to a high proportion of residents seeking moonlighting.[7,8] Studies addressing the relation between resident compensation, financial strain, and moonlighting practice are lacking.

In Brazil, as there are no standards on residents' moonlighting, they can moonlight at any time in residency; however, the moonlighting hours do not count toward the requirement of 60 weekly hours in the residency program. In the United States (US), moonlighting hours must be included in the weekly limit of 80 h, and some programs do not allow or have specific standards for moonlighting.[2,3]

Research has been conducted on residency program duty hours and their negative impacts on residents' health.[9,10] However, data have related moonlighting to a better quality of life and satisfaction with work-life balance, as well as to reduced frequencies of stress and burnout.[3,11,12] It is important to improve comprehension of these conflicting observations. Understanding the

motivations for moonlighting practice, and its consequences on both residents' learning and patient safety is warranted. Nonetheless, this is a poorly explored subject worldwide, and data on moonlighting and its related factors are scarce.

OBJECTIVE

This study aimed to describe the frequency of moonlighting among a nationwide multi-specialty sample of physician residents in Brazil, as well as the related factors. Further, we aimed to analyze residents' perceptions of the "fairness" of the current compensation they received.

METHODS

This cross-sectional study enrolled a nationwide sample of medical residents from Brazil between November and December 2019. We developed and performed face validation, tested the questions for comprehension with a pilot of 20 residents, and assessed the ease-of-use of the final tool. We then conducted an online survey called, "How is your medical residency going?," which aimed to assess general questions about residency training, using 46 questions over four pages. This was the first study to enroll residents from all regions of Brazil and was primarily exploratory. Details and primary analyses of this study have already been published.[13,14]

The questionnaire was outreached on social networks (Facebook and Instagram, in pages/profiles of medical residents' associations). To ensure that only medical residents answered the survey, we had an obligatory button, "I confirm that I am a medical resident currently," displayed before the questionnaire.

The STROBE reporting guidelines were followed in this study. The Ethics Committee of Universidade Federal de Pernambuco (UFPE) approved this study before data collection (Approval number: 3.314.833 on May 9, 2019). All individuals provided consent, and no benefits were offered or given to participate.

Moonlighting

Moonlighting was defined as performing any paid medical activity unconnected to residency program requirements. We examined the frequency and type (oncalls or outpatient care) of this activity. According to Brazilian laws, medical residents are allowed to moonlight at any time during residency training; moonlighting hours are not included in the residency program duty hours.

Residency salary

We enquired regarding the residency salary (monthly financial value received by the residents from the institutions that provide the residency program) on two topics. Residents' judgment on the amount received (Is the current value of the residency salary fair/adequate?); and the residents' judgment on how much amount would be appropriate (what would be the fair/adequate value of the residency salary?).

In case of individuals who practiced moonlighting, we also asked about the impact of a hypothetical scenario in which they received the amount believed to be "fair/adequate" (if you received the amount mentioned in the previous question, what would you do about moonlighting?). All questions were closed-ended.

Psychological distress

Validated tools were used to measure anxiety, depression, and diurnal somnolence. Patient Health Questionnaire-4 (PHQ-4) is a screening method using four Likert-type questions (two for depression and two for anxiety), with scores ranging from 0 to 3 (higher scores indicate a higher chance of these conditions). Individuals who scored ≥ 3 had a positive screening result for a specific condition.

Day-time sleepiness was assessed using the six-item Brazilian version of Epworth Sleepiness Scale, each Likert-type question score ranged from 0 to 3 (higher scores indicated higher diurnal somnolence). Individuals who scored ≥ 10 had positive screening results for diurnal somnolence.

Work-personal life conflicts were assessed by the affirmation "My routine in this medical residency program allows me enough time for my personal and family activities." It was a five-item Likert-type response ranging from "strongly disagree" to "strongly agree." Individuals who answered "strongly disagree" or "disagree" were classified as having work-personal life conflicts.

Residency program and socio-demographic aspects

We included questions on residency program characteristics (duty hours, training area [clinical, surgical, or diagnostic], post-graduate year [PGY], and geographic region of training). Personal data included age, sex, marital and child status, and weekly leisure hours (time spent with himself/herself [hobbies, physical exercises, beauty care, etc.]). We questioned whom the residents lived with, and if they had to move to participate in the residency program.

Statistical analysis

According to the responses to moonlighting questions, individuals were categorized into the moonlighting (any type or workload) or control (no reported moonlighting at all) groups.

Discrete variables are expressed as mean and standard deviation, and comparisons between the two groups were performed with Mann–Whitney or student's t-test, according to parametric distribution (Kolmogorov–Smirnov test). For comparisons between more than two groups, we applied the Kruskal–Wallis test with Dunn's correction. Qualitative variables are expressed as

percentages, and contingency analyses were conducted using the Chi-square test. Correlations were expressed using Spearman's rho.

To analyze independent (dichotomized or discrete) variables affecting moonlighting, we applied binary logistic multiple regression. Poisson regression model was used to assess factors influencing the compensation that residents stated they should receive. All variables with $P < 0.20$ in bivariate analysis were included in the model, and a backward stepwise process was performed (excluding the factors with higher P-values on Wald test) until all factors were at $P < 0.05$.

Once all answers were obtained to go ahead with the survey (except those that might identify the volunteers), our missing data were low (< 0.1%). Individuals with missing data were excluded from specific analyses. For sensitivity analyses, we identified multivariate outliers using the Mahalanobis test, excluded those individuals (n = 43), and reanalyzed the data.

All analyses were performed using SPSS (Armonk, New York, United States) v25 for MacOS. A P value of 0.05 was considered statistically significant for all analyses. We did not calculate the sample size before data collection.

RESULTS

Our link received 1,989 clicks, of which 1,421 individuals completed the survey (71.4% completion rate). Two participants were excluded because of conflicting answers (n = 1,419).

Study population

Our sample was composed of 535/1,419 (37.7%) males, with a mean age of 28.8 ± 3.2 years. Majority had no children (1,292/1,419, 91.1%), were single (978/1,419, 68.9%), and needed to move to participate in residency (913/1,419, 64.3%). Regarding residency-related aspects, 40.2% (571/1,419) were PGY-1, 29.7% were PGY-2, and 30.1% were PGY-3 or higher. The clinical training area was the most common (736/1,419, 51.9%), followed by surgical (43.0%), and diagnostic (5.1%).

Moonlighting

Majority (1,140/1,419, 80.3%) of the residents practiced moonlighting, with an average weekly workload in these activities of 14.1 ± 9.4 h. **Table 1** compares the socio-demographic data according to moonlighting status.

Variables independently related to moonlighting were being PGY-2 or higher, lower weekly residency duty hours (a mean difference of 6.2 h, $P < 0.001$), and considering higher values of salary as "fair/adequate." Moreover, individuals who did moonlight were older, non-single, male, and parents, and had a slightly longer leisure time (mean difference of 1.0 h, $P = 0.002$) than those who did not, although these did not persist after adjustment for confounders.

Epworth sleepiness, PHQ-4 scores, and frequency of work-personal life conflicts did not differ between the groups. It is worth mentioning that the frequency of positive screening was high.

The residents generally moonlighted overnight and/or in weekend shifts (1,100/1,140, 96.5%), but almost one-quarter (267/1,140, 23.4%) practiced outpatient care. **Table 2** depicts these data and the residents' judgments regarding salary values.

Residency salary perception

Most residents (1,412/1,418, 99.5%) believed that the compensation they received was not "fair/adequate". The main

Table 1. Bi- and multivariate analysis of demographic, psychological distress, and program-related characteristics, according to moonlighting status

Variables*	Moonlighting (n = 1,140)	Controls (n = 279)	P	aOR (95% CI)	P
Moonlighting**	14.1 ± 9.4	-	-	-	-
Age	29.0 ± 3.2	28.0 ± 2.9	< 0.001	-	-
Male sex	443 (39.4)	92 (33.2)	0.062	-	-
Have child/children	111 (9.7)	16 (5.7)	0.035	-	-
Single	765 (67.1)	213 (76.3)	0.003	-	-
Moved to take this residency training	724 (63.5)	189 (67.7)	0.209	-	-
Live alone	431 (37.8)	109 (39.1)	0.731	-	-
Geographic area, South	773 (67.8)	199 (71.3)	0.281	-	-
Post-graduation year 2 or higher	757 (66.4)	88 (31.5)	< 0.001	3.90 (2.93–5.18)	< 0.001
Residency duty**	68.8 ± 14.9	75.0 ± 18.8	< 0.001	.98 (0.97–0.98)	< 0.001
Clinical training area	613 (53.8)	123 (44.1)	0.004	-	-
Leisure time**	7.4 ± 6.5	6.4 ± 6.6	0.002	-	-
Work-personal life conflicts	891 (78.2)	212 (76.0)	0.424	-	-
Epworth sleepiness positive screen	715 (62.7)	181 (64.9)	0.534	-	-
PHQ-4 positive screen	564 (49.5)	135 (48.4)	0.789	-	-
"Fair" value of salary#	6.9 ± 1.9	6.5 ± 1.9	0.002	1.23 (1.08–1.40)	0.002

OR = odds ratio; CI = confidence interval; PHQ-4 = Patient Health Questionnaire-4. aOR = adjusted odds ratio.*mean±standard deviation, or n (%). **Hours per week; #value in thousand reais (Brazilian currency). aOR refers to logistic regression model. Sensitivity analysis did not significantly change the results.

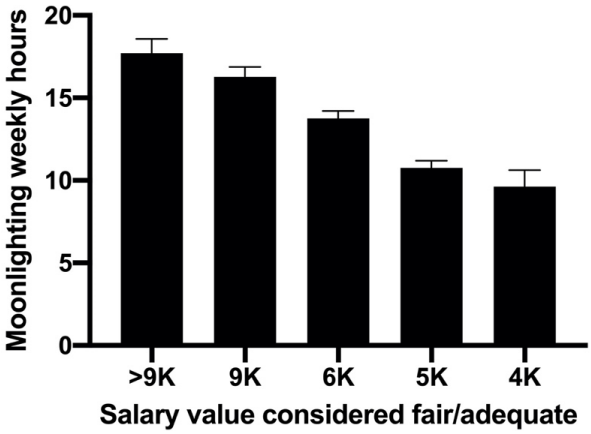
reasons for this are described in **Table 2**, which included "high workload" (84.1%), "complexity of the tasks performed" (67.6%), and "insufficient value to support him/herself" (63.3%).

The mean "fair" value was considered to be R$ 6.8 ± 2.0 thousand per month (equivalent to US$ 19,245 per year, considering the exchange at the time of data collection).

We found positive correlations between how much would be the "fair/adequate" salary and the weekly duty hours spent practicing moonlighting (rho = 0.273, 95% confidence interval [CI] = 0.216–0.328, P < 0.001, **Figure 1**), and the number of motives to justify the "unfairness" of the current compensation (rho = 0.261, 95% CI = 0.210–0.310, P < 0.001).

Regarding the hypothetical scenario in which residents who practice moonlighting would receive the compensation cited as "fair/adequate," majority (783/1,140, 68.7%) reported that they would stop moonlighting, and only 1.5% would not change their moonlighting routine in this situation.

In Poisson regression model, the compensation value reported as "fair/adequate" was influenced by higher age (1.02 [95% CI = 1.01–1.02], P < 0.001), longer residency duty hours (1.51 [1.22–1.88], P < 0.001), and not being single (1.05 [1.01–1.10], P = 0.024).



Bars indicate the mean and lines indicate standard error. Between-group comparisons showed P < 0.001 (Kruskal–Wallis test). Dunn's test for multiple comparisons showed adjusted P < 0.001 for all pairs, except for 5K-4K and > 9K-9K, which had P > 0.05. When both variables were assessed as discrete, rho = 0.273 (95% confidence interval [CI] = 0.216–0.328, P < 0.001). Sensitivity analysis did not significantly change the results.

Figure 1. Compensation value considered fair/adequate by the residents in relation to mean moonlighting hours per week (n = 1.140).

Table 2. Frequency of moonlighting, perception of the value of the medical residency salary, and the impact of a possible adjustment of the salary value on moonlighting

Variable	Result (n, %)
Type of moonlighting*	
Overnight and/or weekend shifts	1,100 (77.5)
Outpatient care	267 (18.8)
No moonlighting	279 (19.7)
Is the current value of the residency salary fair/adequate?*	
No, because it does not match with my quantity of working hours	1194 (84.1)
No, because it is not proportional to the complexity of the tasks/activities that I perform	959 (67.6)
No, because it is not enough to support myself	898 (63.3)
No, because it is not equivalent to the income of other governmental programs, such as "MaisMédicos"**	749 (52.8)
No, because it is not equivalent to the income of the other medical staff	308 (21.7)
Yes, because the hospital has additional costs to having residents	10 (0.7)
Yes, because it is enough to support myself	7 (0.5)
What would be the fair/adequate value of the residency salary?	
The current value is fair	7 (0.5)
1/3 more (about 4 thousand reais)	67 (4.7)
2/3 more (about 5 thousand reais)	362 (25.5)
Double (about 6 thousand reais)	482 (34.0)
Triple (about 9 thousand reais)	344 (24.2)
More than the triple	157 (11.1)
If you received the amount mentioned in the previous question, what would you do about moonlighting?†	
I would not work in any moonlighting, at all	783 (68.7)
I would decrease my quantity of moonlighting	340 (29.8)
I would not change my routine of moonlighting	17 (1.5)

*The sums are greater than 1419, because each individual could check more than one option.**A Brazilian governmental program intended to increase the number of physicians around Brazilian territory.
†Individuals who do moonlighting (n = 1.140).

DISCUSSION

This is the first study addressing moonlighting and related factors in Brazil, and the first in the world correlating moonlighting workload to salary perceptions. Our data show that more than 80% of residents moonlight, and the time spent in these activities is high (approximately 14 h per week). Moonlighting was related to higher PGY, briefer residency duty hours, and considering higher values of remuneration as "fair/adequate." Almost all (99.5%) surveyed residents thought that the current Brazilian residency salary is not "fair/adequate," mainly because of the high workload and complexity of the tasks performed. Moonlighting was not associated with psychological distress. These data shed some light on understanding of effort-reward imbalance in residents, moonlighting practices, and related factors.

In line with our data, other studies[15,16] have shown that a higher PGY increases the odds of moonlighting. We hypothesized that the confidence and skills obtained during residency training, in tandem with the professional relationships built in this process, are central factors in opting for moonlighting. Moreover, working hours of PGY-1 are usually longer,[16] which hampers this possibility. However, we did not find significant differences in moonlighting practice and specific areas of training (clinical versus surgical or diagnostic areas), which is different from others.[11]

The moonlighters expected higher compensation values. We found an association between expected compensation and moonlighting workload, and a significant proportion (98.5%) of residents stated that in a hypothetical scenario of receiving a "fair/adequate" residency program salary, they would stop or reduce duty hours in moonlighting. In addition, moonlighters have a higher chance of having children and being married. The hypothesis that perceived financial strain (present or future, presumed) is the main cause of moonlighting, appears to fit our model. Indeed, studies have shown that moonlighting increases income,[2,17] and a large section of literature agrees with that.[1,14,18-20] In contrast, it is worth noting that there are other motivations for moonlighting, such as maximizing learning, getting autonomy and experience, and improving procedural skills.[1,11,15,19]

The frequency of moonlighting depends on other factors beyond those mentioned above, such as specialty and hospital demands[21] and workload of residency program training.[16] The mean moonlighting duty hours per week found by us (mean 14.1 h) were far higher than that in the US literature (average 4 to 8 h,[1,3] although one study pointed to 20.2 h in a small sample of surgical residents),[19] probably owing to the longer (80 h compared to 60 h in Brazil) duty hours requirement in the US.

Individuals who did not practice moonlighting had higher workload in the residency program (however, both groups had mean duty hours higher than Brazilian standards) and less leisure time. High-intensity training programs may hinder residents from engaging in moonlighting and leisure activities, but we did not assess this program's aspect. We believe that PHQ-4 scores and the frequency of diurnal somnolence and work-personal life conflicts were similar between the groups because of the counterbalancing effect of those factors. Some studies have found that moonlighters have a better quality of life and work-life balance,[12] as well as smaller frequencies of burnout[17]and stress,[11] although others did not.[3,14] Poor sleeping patterns due to moonlighting were not observed, although some data[2] pointed it as the main issue of moonlighting.

Perhaps individuals more prone to moonlighting consider the presumed training workload when opting to join a specific specialty or hospital.[11] Another possibility is that individuals who cope better with residency demands have a higher chance of engaging in moonlighting; these hypotheses are not mutually exclusive. However, these interactions should be cautiously interpreted. Moreover, the impact of moonlighting on patient safety, frequency of medical errors, and residents' learning is not fully understood. We found studies that did not find differences in objective[22] or subjective[23] evaluations of learning regarding moonlighting status.

It should be mentioned that the perception of the "fair/adequate' value of salary depended on higher age, not being single, and longer residency duty hours.

Main reasons for considering the current value "inadequate/unfair" were, indeed, the quantity (reflected on duty hours) and complexity of the tasks performed, configuring an effort-reward imbalance setting. It is worth noting that the cited workload of moonlighting pays, on average, what most residents said it would be fair to receive (i.e., an additional 66% to 100% of the current compensation);[24] and that higher age and not being single may be related to the need for a higher income – this aspect has already been described[11,16] and may be a motivation for moonlighting.

Our study had several limitations. It was outreached in pages of the Brazilian Association of Residents on social networks; hence, it was a convenience sample, and we might have a selection bias. However, our sample is similar to census data[25] regarding age, sex, area of training, and geographic distribution. According to this census[25], the total number of medical residents in 2018 was 35,187; we achieved 4.0% of this population. Nevertheless, it is worth mentioning that this sample could not be reached by our approach. We could not control the number of responses provided by a specific participant in this survey. All variables were self-reported. We did not ask about the debt burden; hence, we were not able to assess its relationship with moonlighting.

CONCLUSION

Moonlighting frequency is high and is related to higher PGY, briefer residency duty hours, and the perception that the salary should be higher. Most residents think that they earn compensation lower than deserved, based on the high workload and

complexity of the tasks performed. The "fair/adequate" value of the salary was associated with higher age, not being single, and longer residency duty hours.

This study provides insights into the motivations for moonlighting and effort-reward imbalance among residents. The impact of moonlighting on the learning of residents and patient safety should be addressed in further studies.

REFERENCES

1. Vogt HB, Huntington MK. Influence of Resident Physician "Moonlighting" Activities on Educational Experience and Practice Choice. S D Med. 2015;68(8):351-5. PMID: 26380429.
2. Saxon JT. Moonlighting: Pros and Cons for Fellows. J Am Coll Cardiol. 2015;65(2):214-6. PMID: 25593064; https://doi.org/10.1016/j.jacc.2014.11.020.
3. Benson NM, Beach SR. After Hours: A Survey of Moonlighting Practices in Psychiatry Residents. Acad Psychiatry. 2019;43(1):18-22. PMID: 30414071; https://doi.org/10.1007/s40596-018-1003-6.
4. Peru. Decreto Peruano de Valorizacion Principal a favor de los Organismos Públicos del Ministerio de Salud [Internet]. 2018. Available from: https://www.mef.gob.pe/es/por-instrumento/decreto-supremo/17054-decreto-supremo-n-006-2018-ef/file. Accessed in 2022 (Jul 11).
5. Agudelo J. Médico residente: este es el nuevo salario que recibirá a partir del año 2020 [Internet]. 2019. Available from: https://noticias.canal1.com.co/nacional/medico-residente-este-es-el-nuevo-salario-que-recibira-a-partir-del-ano-2020/. Accessed in 2022 (Jul 11).
6. Scheffer M, Cassenote A, Guerra A, Guilloux AGA, Drulla APB. Demografia Médica no Brasil 2020. São Paulo: Conselho Federal de Medicina; 2020.
7. Araújo AL de SLC, Arar FC, Moura EP. Avaliação da Qualidade de Vida dos Residentes de Ortopedia Brasileiros. Rev Bras Educ Med. 2019;43(1 suppl 1):219-27. https://doi.org/10.1590/1981-5271v43suplemento1-20190105.
8. Dias BA, Pereira MN, Sousa IF de, Almeida RJ de. Qualidade de vida de médicos residentes de um hospital escola. Sci Med (Porto Alegre). 2016;26(1):22315. https://doi.org/10.15448/1980-6108.2016.1.22315.
9. Parshuram CS, Amaral AC, Ferguson ND, et al. Patient safety, resident well-being and continuity of care with different resident duty schedules in the intensive care unit: a randomized trial. CMAJ. 2015;187(5):321-9. PMID: 25667258; https://doi.org/10.1503/cmaj.140752.
10. Busireddy KR, Miller JA, Ellison K, et al. Efficacy of Interventions to Reduce Resident Physician Burnout: A Systematic Review. J Grad Med Educ. 2017;9(3):294-301. PMID: 28638506; https://doi.org/10.4300/JGME-D-16-00372.1.
11. Baldwin DC Jr, Daugherty SR. Moonlighting and Indebtedness Reported by PGY2 Residents: it's not just about money!Acad Med. 2002;77(10 Suppl):S36-8. PMID: 12377699; https://doi.org/10.1097/00001888-200210001-00012.
12. West CP, Shanafelt TD, Kolars JC. Quality of Life, Burnout, Educational Debt, and Medical Knowledge Among Internal Medicine Residents. JAMA. 2011;306(9):952-60. PMID: 21900135; https://doi.org/10.1001/jama.2011.1247.
13. de Mélo Silva Júnior ML, Melo TS, de Sousa Menezes NC, Valença MM, Sampaio Rocha-Filho PA. Headache in Medical Residents: A Cross-Sectional Web-Based Survey. Headache. 2020;60(10):2320-9. PMID: 33118613; https://doi.org/10.1111/head.14000.
14. de Mélo Silva Júnior ML, Valença MM, Rocha-Filho PAS. Individual and residency program factors related to depression, anxiety and burnout in physician residents - a Brazilian survey. BMC Psychiatry. 2022;22(1):272. PMID: 35436910; https://doi.org/10.1186/s12888-022-03916-0.
15. Robinson LA, Osborne LM, Hsu AJ, Park H, Arbuckle MR. Moonlighting by Psychiatry Residents: a Survey of Residents and Training Directors. Acad Psychiatry. 2019;43(1):46-50. PMID: 30456706; https://doi.org/10.1007/s40596-018-1004-5.
16. Baldwin DC Jr, Daugherty SR, Tsai R, Scotti MJ Jr. A National Survey of Residents' Self-Reported Work Hours: Thinking Beyond Specialty. Acad Med. 2003;78(11):1154-63. PMID: 14604880; https://doi.org/10.1097/00001888-200311000-00018.
17. McNeeley MF, Perez FA, Chew FS. The Emotional Wellness of Radiology Trainees: prevalence and predictors of burnout. AcadRadiol. 2013;20(5):647-55. PMID: 23570939; https://doi.org/10.1016/j.acra.2012.12.018.
18. Steiner JW, Pop RB, You J, et al. Anesthesiology Residents' Medical School Debt Influence on Moonlighting Activities, Work Environment Choice, and Debt Repayment Programs. AnesthAnalg. 2012;115(1):170-5. PMID: 22366844; https://doi.org/10.1213/ANE.0b013e318248f61d.
19. Jamshidi R, Reilly LM. Surgical Residents'Clinical Activity During Research: Shedding Light on Moonlighting Practices. J Surg Educ. 2008;65(6):486-93. PMID: 19059182; https://doi.org/10.1016/j.jsurg.2008.05.003.
20. Glaspy JN, Ma OJ, Steele MT, Hall J. Survey of Emergency Medicine Resident Debt Status and Financial Planning Preparedness. AcadEmerg Med. 2005;12(1):52-6. PMID: 15635138; https://doi.org/10.1197/j.aem.2004.02.532.
21. Baldwin DC Jr, Daugherty SR, Ryan PM, Yaghmour NA. What Do Residents Do When Not Working or Sleeping? A Multispecialty Survey of 36 Residency Programs. Acad Med. 2012;87(4):395-402. PMID: 22361798; https://doi.org/10.1097/ACM.0b013e318249638b.
22. Mirkes C, Myers JD, Song J, et al. Examining the Relationship Between Internal Medicine Resident Moonlighting and IM-ITE Performance. Am J Med. 2014;127(2):163-7. PMID: 24332727; https://doi.org/10.1016/j.amjmed.2013.10.014.
23. Mélo Silva Júnior ML, Valença MM, Sampaio Rocha-Filho PA. Characteristics of residency programs and residents' learning experience in Brazil: a multispecialty, nation-wide study. Psychol Health Med. 2022;1-12. PMID: 35773980;
24. SanarUP. Afinal, quanto ganha um médico recém-formado? 2020. Available from: https://www.sanarmed.com/afinal-quanto-ganha-um-medico-recem-formado. Accessed in 2022 (Jul 11).

25. Demografia Médica no Brasil/Coordenação de Mário Scheffer; equipe de pesquisa: Alex Cassenote, Aline Gil Alves Guilloux, Aureliano Biancarelli, Bruno Alonso Miotto e Giulia Marcelino Mainardi. – 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, 2018. Available from: https://jornal.usp.br/wp-content/uploads/DemografiaMedica2018.pdf. Accessed in 2022 (Jul 11).

Authors' contributions: Silva-Júnior MLM: conceptualization (lead), formal analysis (lead), methodology (equal), writing-original draft (lead); Rocha-Filho PAS: conceptualization (supporting), methodology (supporting), supervision (equal), and writing-review and editing (equal). All authors actively contributed to the discussion of the study results and all reviewed and approved the final version to be published

Sources of funding: This study did not receive any grants or funding
Conflicts of interest: All the authors declare that they have no conflict of interests

Date of first submission: March 24, 2022
Last received: July 1, 2022
Accepted: August 23, 2022

Address for correspondence:
Mário Luciano de Mélo Silva Júnior
Universidade Federal de Pernambuco (UFPE)
Av. Moraes Rego, 1.235
Cidade Universitária — Recife (PE) — Brasil
CEP 50670-901
Tel. (+55 81) 2126-8539
E-mail mariomelosjr@gmail.com

Clinical and laboratory differences between chromosomal and undefined causes of non-obstructive azoospermia: A retrospective study

Luísa Riccetto[I], Tarsis Paiva Vieira[II], Nilma Lucia Viguetti-Campos[III], Tais Nitsch Mazzola[IV], Mara Sanches Guaragna[V], Helena Fabbri-Scallet[VI], Maricilda Palandi de Mello[VII], Antonia Paula Marques-de-Faria[VIII], Andrea Trevas Maciel-Guerra[IX], Gil Guerra-Junior[X]

Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Hospital das Clínicas da Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil

[I]Undergraduate Medicine Student, Pontifícia Universidade Católica de Campinas (PUCCAMP), Campinas (SP), Brazil; and Member, Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-0154-2218

[II]PhD. Professor, Department of Translational Medicine, School of Medical Sciences, Laboratory of Human Cytogenetics, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-4027-8341

[III]PhD. Laboratory Worker, Department of Medical Genetics Genomics, School of Medical Sciences, Laboratory of Cytogenetics, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0001-8452-1935

[IV]PhD. Laboratory Worker, Laboratory of Human Molecular Genetics, Center of Molecular Biology and Genetic Engineering, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-4701-7734

[V]PhD. Researcher, Laboratory Worker, Laboratory of Human Molecular Genetics, Center of Molecular Biology and Genetic Engineering, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-6508-8571

[VI]PhD. Researcher, Laboratory Worker, Laboratory of Human Molecular Genetics, Center of Molecular Biology and Genetic Engineering, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-2738-1814

[VII]PhD. Professor, Laboratory of Human Molecular Genetics, Center of Molecular Biology and Genetic Engineering, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-0521-9100

[VIII]PhD. Professor, Department of Medical Genetics and Genomics Medicine, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP); and Member, Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-5454-8982

[IX]PhD. Professor, Department of Medical Genetics and Genomics Medicine, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP); and Member, Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS) Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-4850-8079

[X]PhD. Professor, Department of Pediatrics, School of Medical Sciences Universidade Estadual de Campinas (UNICAMP); and Member, Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-2991-7678

KEYWORDS (MeSH terms):
Sperm count.
Infertility.
Gonadotropins.
Disorders of sex development.

AUTHORS' KEYWORDS:
Arm span.
Height.
Sexual development disorders.

ABSTRACT

BACKGROUND: Knowledge of clinical and laboratory differences between chromosomal and undefined causes aids etiological research on non-obstructive azoospermia.

OBJECTIVE: Compare clinical and laboratory differences between men with non-obstructive azoospermia due to chromosomal anomalies versus undefined causes

DESIGN AND SETTING: A cross-sectional retrospective study conducted at a public university hospital in Campinas (Brazil)

METHODS: All men aged 20–40 years with non-obstructive azoospermia were included in the analysis.

RESULTS: The 107 cases included 14 with Klinefelter syndrome (KS) (13%), 1 with mosaic KS, 4 with sex development disorders (2 testicular XX, 1 *NR5A1* gene mutation, and 1 mild androgen insensitivity syndrome) (4%), 9 with other non-obstructive azoospermia etiologies (8%), and 79 with undefined causes. The 22 chromosomal anomaly cases (14 KS, 1 mosaic KS, 2 testicular XX, 4 sex chromosome anomalies, and 1 autosomal anomaly) were compared with the 79 undefined cause cases. The KS group had lower average testicular volume, shorter penile length, and lower total testosterone levels but greater height, arm span, serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and gynecomastia frequency (absent in the undefined group and affecting more than half of the KS group). Patients with testicular XX DSD had LH, FSH, and penile length data intermediate between the KS and undefined cause groups, testicular volume similar to the KS group, and other data similar to the undefined group.

CONCLUSION: Clinical and laboratory data differentiate men with non-obstructive azoospermia and chromosomal anomalies, particularly KS and testicular XX, from those with undefined causes or other chromosomal anomalies.

INTRODUCTION

Male infertility is defined as the biological inability of a man to induce pregnancy in a fertile woman after unprotected sexual intercourse for at least one year.[1] A study of a North American population revealed that 12% of male individuals aged 15–44 years are infertile.[2] The main factors related to infertility include obesity, infection, neoplasms, cryptorchidism, smoking, varicocele, chromosomal anomalies, sperm duct defects, scrotal exposure to high temperatures, hormonal imbalances, celiac disease, medications, heavy metal poisoning, and exposure to ionizing radiation.[3-5]

Regarding the genetic causes of male infertility, approximately 15–20% of men with severe non-obstructive azoospermia or oligospermia have microdeletions on the long arm of the Y chromosome (AZFa, b, or c regions) where the spermatogenesis genes are located.[6,7] Some cases of male infertility may also be related to disorders of sex development (DSD), such as Klinefelter syndrome (KS), testicular 46,XX DSD, and disorders related to the synthesis or action of testicular hormones.[8]

Currently available DSD cohorts in the literature mostly include pediatric patients, with genital ambiguity being the main reason for referral.[9,10] In contrast, studies of genetic causes of male infertility have mainly focused on chromosomal anomalies and Yq microdeletions.[11,12] In these studies, as well as in the guidelines on male infertility,[3] DSD are not specifically considered a cause.

A recent study by our group of 84 men with non-obstructive infertility (azoospermia or severe oligospermia) showed that 10 (12%) had KS, 1 had testicular DSD 46,XX, and 1 had mild

androgen insensitivity syndrome (MAIS). The same study also observed 4 cases of structural anomalies of the Y chromosome, 2 Yq microdeletions, and 1 autosomal anomaly corresponding to 22% of the evaluated cases. Of total patients studied, only 14 had increased serum FSH levels, 23 had increased FSH and LH levels, and 13 had decreased testosterone levels.[13]

Considering that about one-fourth of men with severe infertility have chromosomal anomalies and that the clinical and laboratory characteristics of these men, compared to those without chromosomal anomalies, have been insufficiently studied in the literature, it is necessary to verify whether these data can be useful for distinguishing men with chromosomal anomalies from those without a clear cause of their non-obstructive azoospermia.

OBJECTIVE

To compare clinical and laboratory data of men with non-obstructive azoospermia due to chromosomal anomalies versus undefined causes.

METHODS

Population data

This observational cross-sectional retrospective study was based on a medical record analysis. All included patients received medical care from the Interdisciplinary Group for the Study of Sex Determination and Differentiation (Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo, GIEDDS) at the Hospital das Clínicas da Universidade Estadual de Campinas (HC-UNICAMP), in Campinas, Sao Paulo, Brazil. This study included all men aged 20–40 years with non-obstructive azoospermia (absence of sperm in the ejaculate secondary to impaired spermatogenesis) who were referred to our outpatient clinic for etiological clarification between January 2010 and December 2019. The inclusion criteria were non-obstructive azoospermia (confirmed by at least two sperm counts) and no history of medication use or a disease recognized as a possible cause of male infertility. The exclusion criterion was incomplete clinical and/or laboratory data in the medical records. The project was approved by the Institution's Research Ethics Committee (CAAE: 31480020.0.0000.5404) on June 2, 2020.

Clinical data

The following clinical data were obtained from the patients' medical records: age (years), auto-declared race (white, brown, black, yellow, other), family history (e.g., parental consanguinity or recurrence of infertility within the family, which was considered positive if there were male relatives as far as third cousins who did not induce spontaneous pregnancies), educational status (illiterate, complete elementary and middle school or 8 years, complete high school or 11 years, or undergraduate school completed or not), height (cm), difference from average family target height,[14] arm span (cm) and ratio to height, body mass index (BMI) in kg/m^2, penile length (in cm),[15] and testicular volume (in mL).

Laboratory and genetic data

In all cases, a conventional G-banding karyotype study was performed with 400-band resolution and a minimum count of 20 metaphases. In those with normal karyotypes, analysis of a Yq microdeletion was performed using the polymerase chain reaction multiplex technique and 28 molecular markers that mapped the three regions considered the azoospermia locus (AZFa, AZFb, and AZFc).

The following laboratory data were also obtained from the medical records: LH (IU/L), FSH (IU/L), and total testosterone (ng/mL) serum concentrations, karyotype data, Yq microdeletion data, and other cytogenetic or molecular tests.

Statistical analysis

The statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 20.0, Chicago, USA applying absolute and relative frequency data using the Mann-Whitney and Fisher tests with a level of significance of $P < 0.05$.

RESULTS

A total of 150 cases were evaluated, but only 107 met the inclusion criteria: 14 with KS, 1 with mosaic KS (47,XXY/46,XY), 4 with other sex chromosome anomalies [1 with 47,XYY; 1 with 46,X,idic(Yq); 1 with 46,X,del(Y)(q12); 1 with 46,X,inv(Y)(p11.2q11.23)], 1 with autosomal anomaly [46,XY,t(6;13)(p12;p13)], 2 with Yq microdeletion, 2 with autosomal recessive infertility with increased FSH and no mutation in the *FSHR* gene, 1 with MAIS and confirmed mutation in the *AR* gene, 2 with testicular 46,XX DSD, 1 with mutation in the *NR5A1* gene, and 79 with undefined cause. In the defined cause group, the cases of KS, mosaic KS, MAIS, *NR5A1* mutation, and testicular XX were considered DSD (i.e., 19 of 107 [17.7%]), with chromosomal anomalies in KS, mosaic KS, testicular XX, and other autosomal or sex chromosome anomalies (22 of 107 [20.6%]). Of these 107 cases, 101 were included in this study, of which 79 had undefined causes and 22 had chromosomal anomalies (**Table 1**). Patients with a defined cause of non-obstructive azoospermia but no chromosomal abnormalities (2 with Yq microdeletion, 2 with autosomal recessive infertility with increased FSH and no mutation in the *FSHR* gene, 1 with MAIS and confirmed mutation in the *AR* gene, and 1 with mutation in *NR5A1* gene) were excluded.

Among the 101 cases, the mean age was 30.4 years (SD: 4.8 years; range, 22–40 years); the auto-declared race was white for

67, brown for 20, and black for 15; and the educational status was illiterate for 11, completed elementary and middle school for 53; completed high school for 27, and undergraduate school for 10. No characteristics (age, race, or educational status) differed between those with KS, mosaic KS, sex chromosome and autosomal anomalies, testicular XX, and undefined etiologies. Obesity was present in 42 patients, although the data did not differ between the groups.

Due to the small number of cases in some of these groups, we decided to compare only the data between the 14 patients with KS and 79 patients in the undefined cause group.

There was no statistically significant difference (Mann-Whitney test) between the KS group (n = 14) and the undefined group (n = 79) in parental height (P = 0.37), arm span and height ratio (P = 0.98), or BMI (P = 0.15) (**Table 1**). However, a statistically significant difference was observed in mean testicular volume (P < 0.0001), penile length (P < 0.001), and total testosterone level (P < 0.001), all of which were lower in the KS group, as were stature (P < 0.001), difference between the patient's height and mean parental height (P < 0.0001), arm span (P < 0.01), LH serum concentrations (P < 0.0001), and FSH serum concentrations (P < 0.0001), which were all higher in the KS group (**Table 2**). A significant difference was observed in the presence of gynecomastia between the KS and undefined groups; it was absent in the undefined cause group and present in more than half of the KS patients (**Table 2**) (Fisher test, P < 00001). The only other case of gynecomastia was the MAIS patient.

The mosaic KS patient exhibited laboratory data (LH, FSH, and total testosterone) like those of the undefined group as well as average testicular volume, penile length, height, arm span, and BMI, like the KS group (**Table 1**). Patients with testicular XX DSD (n = 2) had LH, FSH, and penile length data intermediate between the KS and undefined cause groups, testicular volume like the KS group, and other data similar to the undefined group (**Table 1**). The data for the remaining cases (other sex chromosomes or autosomal anomalies) did not differ significantly from those of the undefined group.

DISCUSSION

This study determined that approximately 20% of non-obstructive azoospermia cases were associated with chromosomal anomalies or DSD. These results correspond with the percentage reported in the current literature (approximately 15%).[16,17]

KS is the most frequent genetic and chromosomal cause of non-obstructive azoospermia. According to Abramsky and Chapple[18] (1997), approximately 3% of male infertility cases are

Table 2. Clinical and laboratory data of 93 men with non-obstructive azoospermia (14 KS cases, 79 with an undefined etiology)

	KS	Undefined
n	14	79
Penile length (cm)*	9	11
Gynecomastia (n)#	8	0
Test vol (mL)*	4	15
H (cm)*	179	173
PH (cm)	170	169
H – PH (cm)*	9	4
AS (cm)*	183	177
AS/H	1.02	1.02
BMI (Kg/m^2)	28.1	26.2
LH (UI/L)*	21.6	6.8
FSH (UI/L)*	30.5	14.1
Total testosterone (ng/mL)*	2.7	4.5

AS = arm span; BMI = body mass index; FSH = follicle-stimulating hormone; H = height; LH = luteinizing hormone; KS = Klinefelter syndrome; n = number of patients; test vol, average bilateral testicular volume. *Statistically significant difference between the KS and undefined groups (Mann-Whitney test); #statistically significant difference between the KS and undefined groups (Fisher test).

Table 1. Clinical and laboratory data of 101 cases (22 with chromosomal abnormalities, 79 with undefined cause) of men with non-obstructive azoospermia

	KS	KS mos	SCA	AA	Testicular XX	Undefined
n	14	1	4	1	2	79
Penile length (cm)	9	9	11	13	10	11
Gynecomastia (n)	8	0	0	0	0	0
Test vol (mL)	4	20	19	20	5	15
H (cm)	179	178	170	176	172	173
PH (cm)	170	172	168	170	168	169
H – PH (cm)	9	6	2	6	4	4
AS (cm)	183	186	174	175	174	177
AS/H	1.02	1.04	1.02	1.0	1.02	1.02
BMI (kg/m^2)	28.1	28.7	35.9	21.9	23.1	26.2
LH (UI/L)	21.6	3.8	7.3	4.6	11.5	6.8
FSH (UI/L)	30.5	2.8	17.4	1.7	22.0	14.1
Total testosterone (ng/mL)	2.7	4.7	2.2	3.6	5.7	4.5

AA = autosomal anomaly; AS = arm span; BMI = body mass index; FSH = follicle-stimulating hormone; H = height; KS = Klinefelter syndrome; KS mos = mosaic KS; LH = luteinizing hormone; mos = mosaicism; n = number of patients; SCA = sex chromosome abnormality; test vol, mean bilateral testicular volume.

caused by KS. In the present study, 15 of 107 cases (14%) of non-obstructive azoospermia were caused by KS. However, it is important to note that only 25% of KS carriers are diagnosed during their lifetime and that most diagnoses occur in adulthood during patient infertility investigations.[19,20]

Individuals with testicular XX can also be identified among patients with non-obstructive azoospermia. For the most part, these individuals have the *SRY* gene translocated on one of the X chromosomes, and their phenotype is virtually identical to that of individuals with KS. In such cases, the lack of sperm production is due to the absence of other genes on the Y chromosome.[21]

Other autosomal or sex chromosome anomalies can also occur but at a much lower frequency, as observed in the present study. Cases of XY partial gonadal dysgenesis, combined gonadal dysgenesis, and ovotesticular DSD can also be found among individuals with typical or highly virilized male genitalia, which is only detected during adulthood infertility investigations.[22] Other 46,XY DSD that are not associated with gonadal differentiation disorders may also go undiagnosed during childhood and have infertility as their main complaint. This is what often happens in cases of hypogonadotropic hypogonadism, milder forms of testosterone synthesis defects, and also in androgen receptor mutations with a male phenotype (MAIS) or barely noticeable genital ambiguity, in which there is a reduction in sperm production due to defects in androgenic activity.[23,24] Individuals with 5-alpha-reductase type 2 deficiency may also have more pronounced androgenization of the external genitalia which goes undiagnosed in childhood but present as adulthood infertility due to underdevelopment of the prostate and seminal vesicles.[25] In the present study, apart from the KS and testicular XX cases, 1 case of XY partial gonadal dysgenesis due to the *NR5A1* gene mutation and 1 case of MAIS with the *AR* gene mutation were diagnosed. Therefore, the results of the present study show that observation of clinical and laboratory data is very important for the differentiation of cases of non-obstructive azoospermia with chromosomal anomalies or DSD of other etiologies.

Except for the KS and testicular XX cases, the other sex chromosomes and autosomal anomalies did not exhibit clinical or laboratory differences from cases of undefined cause. Few studies in the literature have shown these results.[26,27] However, compared to undefined cases, KS patients presented with smaller testicular volume, shorter penis length, taller stature, greater arm span, higher serum LH and FSH concentrations, and lower testosterone levels. Gynecomastia was absent in the undefined cause group and was present in more than half of the patients with KS. In the literature, testicular volumes lower than 6 mL were present in more than 95% of KS cases,[28] the same being true for increased serum gonadotropins.[28-30] Decreased serum testosterone levels were present in 63–85% of KS cases and occurred more frequently in the older age group.[28-30] Gynecomastia is reportedly present in 38–75% of affected adolescents and adults.[26,28,29] Increased stature occurs in approximately 30% of children and adults with KS.[26,28,31] Smaller penile size is present in 10–25% of children and adults with KS.[26,28] Therefore, although the findings described in the present study are frequent in KS, our data confirm that they are an important tool for differentiating patients with KS from those with other non-chromosomal cases of non-obstructive azoospermia.

The patient with mosaic KS had a laboratory profile similar to that of the undefined group but had clinical features similar to KS with the exception of normal testicular volume. Previous studies demonstrated that it is difficult to pinpoint a specific clinical feature in cases of sex chromosome mosaicism without actually knowing the percentage of each lineage in various tissues, including gonads.[32]

Patients with testicular XX DSD (n = 2) exhibited clinical features similar to those of the undefined group except for decreased testicular volume and hypergonadotropic hypogonadism, but these were not as severe as the results seen in the KS group. Similar data have been described in the literature.[21,33,34]

CONCLUSION

Despite the fact that this study has all the limitations of retrospective data collection, it provides important clinical information that supports medical investigations in men with non-obstructive infertility from a significant sample evaluated homogeneously by a single clinical service over a 10-year period with karyotyping performed in all cases and Yq microdeletions investigated in all patients with a normal karyotype.

Therefore, two main conclusions may be drawn from this study: first, chromosomal anomalies were the cause of approximately 20% of non-obstructive azoospermia cases. Second, clinical and laboratory differences existed among different non-obstructive azoospermia etiologies, especially undefined, KS, and testicular XX cases. For this reason, the results of this study provide an important information resource that will be very useful for physicians and other healthcare professionals during investigations and requests for complementary tests during the etiological evaluation of non-obstructive azoospermia.

REFERENCES

1. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod. 2017;32(9):1786-801. PMID: 29117321; https://doi.org/10.1093/humrep/dex234.
2. Louis JF, Thoma ME, Sørensen DN, et al. The prevalence of couple infertility in the United States from a male perspective: evidence from a nationally representative sample. Andrology. 2013;1(5):741-8. PMID: 23843214; https://doi.org/10.1111/j.2047-2927.2013.00110.x.
3. Jarow J, Sigman M, Kolettis PN, et al. The Optimal Evaluation of the Infertile Male: AUA Best Practice Statement Panel Members: AUA Staff: Consultant; 2010. Available from: https://www.auanet.org/documents/education/clinical-guidance/Male-Infertility-d.pdf. Accessed in 2022 (Sep 8).

4. Olayemi FO. A review on some causes of male infertility. African Journal of Biotechnology. 2010;9(20):2834-42. Available from: https://academicjournals.org/journal/AJB/article-full-text-pdf/1320CE821022. Accessed in 2022 (Sep 8).
5. Katib A. Mechanisms linking obesity to male infertility. Cent European J Urol. 2015;68(1):79-85. PMID: 25914843; https://doi.org/10.5173/ceju.2015.01.435.
6. Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2017;5(7):544-53. PMID: 27395771; https://doi.org/10.1016/S2213-8587(16)30040-7.
7. Krausz C, Cioppi F, Riera-Escamilla A. Testing for genetic contributions to infertility: potential clinical impact. Expert Rev Mol Diagn. 2018;18(4):331-46. PMID: 29540081; https://doi.org/10.1080/14737159.2018.1453358.
8. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015;103(3):e18-25. PMID: 25597249; https://doi.org/10.1016/j.fertnstert.2014.12.103.
9. Balkan M, Tekes S, Gedik A. Cytogenetic and Y chromosome microdeletion screening studies in infertile males with Oligozoospermia and Azoospermia in Southeast Turkey. J Assist Reprod Genet. 2008;25(11-12):559-65. PMID: 18953646; https://doi.org/10.1007/s10815-008-9272-8.
10. Quan Q, Li TJ, Ding XP, et al. Infertility caused by male partners with genetic defects in Sichuan Province of China. Genet Mol Res. 2013;12(4):6512-20. PMID: 24390997; https://doi.org/10.4238/2013.December.11.2.
11. Massart A, Lissens W, Tournaye H, Stouffs K. Genetic causes of spermatogenic failure. Asian J Androl. 2012;14(1):40-8. PMID: 22138898; https://doi.org/10.1038/aja.2011.67.
12. Hotaling J, Carrell DT. Clinical genetic testing for male factor infertility: current applications and future directions. Andrology. 2014;2(3):339-50. PMID: 24711280; https://doi.org/10.1111/j.2047-2927.2014.00200.x.
13. Yabiku RS, Guaragna MS, de Sousa LM, et al. A Search for Disorders of Sex Development among Infertile Men. Sex Dev. 2018;12(6):275-80. PMID: 30372699; https://doi.org/10.1159/000493877.
14. Tanner JM. Fetus into man: physical growth from conception to maturity. Cambridge: Harvard University Press; 1989.
15. Gabrich PN, Vasconcelos JS, Damião R, Silva EA. Penile anthropometry in Brazilian children and adolescents. J Pediatr (Rio J). 2007;83(5):441-6. PMID: 17676248; https://doi.org/10.2223/JPED.1671.
16. Ferlin A, Raicu F, Gatta V, et al. Male infertility: role of genetic background. Reprod Biomed Online. 2007;14(6):734-45. PMID: 17579990; https://doi.org/10.1016/s1472-6483(10)60677-3.
17. Pelzman DL, Hwang K. Genetic testing for men with infertility: techniques and indications. Transl Androl Urol. 2021;10(3):1354-64. PMID: 33850771; https://doi.org/10.21037/tau-19-725.
18. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn. 1997;17(4):363-8. PMID: 9160389; https://doi.org/10.1002/(sici)1097-0223(199704)17:4≤363::aid-pd79≥3.0.co;2-o.
19. Bojesen A, Gravholt CH. Klinefelter syndrome in clinical practice. Nat Clin Pract Urol. 2007;4(4):192-204. PMID: 17415352; https://doi.org/10.1038/ncpuro0775.
20. Tincani BJ, Mascagni BR, Pinto RD, et al. Klinefelter syndrome: an unusual diagnosis in pediatric patients. J Pediatr (Rio J). 2012;88(4):323-7. PMID: 22915094; https://doi.org/10.2223/JPED.2208.
21. Gao X, Chen G, Huang J, et al. Clinical, cytogenetic, and molecular analysis with 46,XX male sex reversal syndrome: case reports. J Assist Reprod Genet. 2013;30(3):431-5. PMID: 23378127; https://doi.org/10.1007/s10815-013-9939-7.
22. Lee PA, Nordenström A, Houk CP, et al. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr. 2016;85(3):158-80. Erratum in: Horm Res Paediatr. 2016;85(3):180. Erratum in: Horm Res Paediatr. 2016;86(1):70. PMID: 26820577; https://doi.org/10.1159/000442975.
23. Hughes IA, Davies JD, Bunch TI, et al. Androgen insensitivity syndrome. Lancet. 2012;380(9851):1419-28. PMID: 22698698; https://doi.org/10.1016/S0140-6736(12)60071-3.
24. Guercio G, Rey RA. Fertility issues in the management of patients with disorders of sex development. Endocr Dev. 2014;27:87-98. PMID: 25247647; https://doi.org/10.1159/000363633.
25. Zhu YS, Imperato-McGinley JL. 5alpha-reductase isozymes and androgen actions in the prostate. Ann N Y Acad Sci. 2009;1155:43-56. PMID: 19250191; https://doi.org/10.1111/j.1749-6632.2009.04115.x.
26. Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Arch Dis Child. 1999;80(2):192-5. PMID: 10325742; https://doi.org/10.1136/adc.80.2.192.
27. Rogol AD. Human sex chromosome aneuploidies: The hypothalamic-pituitary-gonadal axis. Am J Med Genet C Semin Med Genet. 2020;184(2):313-9. PMID: 32170911; https://doi.org/10.1002/ajmg.c.31782.
28. Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab. 2013;98(1):20-30. PMID: 23118429; https://doi.org/10.1210/jc.2012-2382.
29. Salbenblatt JA, Bender BG, Puck MH, et al. Pituitary-gonadal function in Klinefelter syndrome before and during puberty. Pediatr Res. 1985;19(1):82-6. PMID: 3918293; https://doi.org/10.1203/00006450-198501000-00022.
30. Smyth CM, Bremner WJ. Klinefelter syndrome. Arch Intern Med. 1998;158(12):1309-14. PMID: 9645824; https://doi.org/10.1001/archinte.158.12.1309.
31. Vorona E, Zitzmann M, Gromoll J, Schüring AN, Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. J Clin Endocrinol Metab. 2007;92(9):3458-65. PMID: 17579198; https://doi.org/10.1210/jc.2007-0447.
32. Rives N, Joly G, Machy A, et al. Assessment of sex chromosome aneuploidy in sperm nuclei from 47,XXY and 46,XY/47,XXY males: comparison with fertile and infertile males with normal karyotype. Mol Hum Reprod. 2000;6(2):107-12. PMID: 10655452; https://doi.org/10.1093/molehr/6.2.107.

33. Wu QY, Li N, Li WW, et al. Clinical, molecular and cytogenetic analysis of 46, XX testicular disorder of sex development with SRY-positive. BMC Urol. 2014;14:70. PMID: 25169080; https://doi.org/10.1186/1471-2490-14-70.
34. Terribile M, Stizzo M, Manfredi C, et al. 46,XX Testicular Disorder of Sex Development (DSD): A Case Report and Systematic Review. Medicina (Kaunas). 2019;55(7):371. PMID: 31336995; https://doi.org/10.3390/medicina55070371.

Authors' contributions: Riccetto L: study conception, design, data collection, analysis, interpretation; manuscript writing, manuscript final approval; Vieira TAP: cytogenetics tests, discussion the results, manuscript writing; manuscript final approval; Viguetti-Campos NL: cytogenetics tests, discussion the results, manuscript writing, manuscript final approval; Mazzola TN: molecular tests, discussion the results, manuscript writing, manuscript final approval; Guaragna MS: molecular tests, discussion the results, manuscript writing, manuscript final approval; Fabbri-Scallet H: molecular tests, discussion the results, manuscript writing, manuscript final approval; Mello MP: conception, design, molecular tests, discussion the results, manuscript writing, manuscript final approval; Marques-de-Faria AP: conception, design, data collection, analysis, interpretation, manuscript writing, manuscript final approval; Maciel-Guerra AT: conception, design, data collection, analysis, interpretation, manuscript writing, manuscript final approval; and Guerra-Junior G: conception, design, data collection, analysis, interpretation, manuscript writing, manuscript final approval

Sources of funding: Scientific Initiation Scholarship to LR from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (process number: 2020-05538-2)
Conflicts of interest: The authors declare no conflicts of interest

Date of first submission: May 6, 2022
Last received: July 24, 2022
Accepted: August 30, 2022

Address for correspondence:
Gil Guerra-Junior
R. Vital Brasil, 80
Campinas (SP) – Brasil
CEP 13083-888
Tel. (+55 19) 3521-7353
E-mail: gilguer@unicamp.br

ERRATUM

https://doi.org/10.1590/1516-3180.2022.0281.R1.300820221erratum

In the manuscript titled "Clinical and laboratory differences between chromosomal and undefined causes of non-obstructive azoospermia: A retrospective study", DOI number 10.1590/1516-3180.2022.0281.R1.30082022, published in the Sao Paulo Medical Journal - Epub ahead of print:

Where it read:
"Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Hospital das Clínicas da Universidade Estadual de São Paulo (UNICAMP), Campinas (SP), Brazil."

It should read:
"Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Hospital das Clínicas da Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil."

Attitudes and practices in the management of attention deficit hyperactivity disorder among Brazilian pediatric neurologists who responded to a national survey: a cross-sectional study

Marina Estima Neiva Nunes[I], Patricia Aparecida Zuanetti[II], Ana Paula Andrade Hamad[III]

Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto (HCFMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil

[I]MD. Child Neurologist, Department of Neurosciences and Behavioral Sciences, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0002-3873-5956

[II]PhD. Speech and Hearing Therapist, Department Health Sciences, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (HCFMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0002-9847-2246

[III]MD, PhD. Child Neurologist, Department of Neurosciences and Behavioral Sciences, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0002-1884-7264

KEY WORDS (MeSH terms):
Attention deficit disorder with hyperactivity.
Child behavior disorders.
Neurodevelopmental disorders.

AUTHORS' KEY WORDS:
ADHD treatment.
Psychostimulants.
Attention deficit disorder.
Hyperkinetic syndrome.

ABSTRACT

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) has a prevalence of 5.3% among children and adolescents. It is characterized by attention deficit, hyperactivity, and impulsivity.

OBJECTIVE: We aimed to conduct a survey involving pediatric neurologists in the management of ADHD and compare the results with the current literature and guidelines.

DESIGN AND SETTING: Descriptive analytical study of a virtual environment, was used Test of equality of proportions for comparison between two groups of pediatric neurologists (working as specialists for > 6 versus ≤ 6 years), with a significance level of P = 0.05.

METHODS: This cross-sectional study used a virtual questionnaire covering the steps in the diagnosis and treatment of children with ADHD. The inclusion criteria were professionals who had completed their residency/specialization in pediatric neurology and clinical neurologists working in pediatric neurology.

RESULTS: Among the 548 electronic invitations sent, 128 were considered valid. For all participants, the diagnosis was clinically based on the disease classification manuals. Combination treatment promotes improvement of symptoms (96.9%). Among psychostimulants, short-acting methylphenidate was the most commonly prescribed medication (85.2%). Headache was the most common side effect (77.3%). Altogether, 73.4% of the participants requested laboratory tests, 71.1% requested an electrocardiogram, and 42.2% requested an electroencephalogram. Pediatric neurologists working as specialists for ≤ 6 years had more frequent referrals to psycho-pedagogists for diagnosis (P = 0.03).

CONCLUSIONS: The participants complied with clinical guidelines, emphasizing the relevance of diagnostic manuals and treatment guidelines for an eminently clinical situation and enabling uniformity in quality treatment.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a global prevalence of 5.3% among children and adolescents (95% confidence interval [CI], 2.6–4.5).[1,2]

Symptoms of ADHD include inattention and excessive hyperactivity/impulsivity for the age or level of development; with impaired personal, social, and academic functioning. Due to the absence of biomarkers, diagnostic criteria focus on behavioral symptoms.[3] According to the Centers for Disease Control and Prevention, ADHD is the most prevalent neuropsychiatric disorder in childhood and adolescence.[4] It is the most common behavioral disorder encountered by pediatric neurologists in clinical practice.[1]

OBJECTIVE

We aimed to conduct a survey involving pediatric neurologists to obtain information on diagnostic and therapeutic management of ADHD and to compare the results with the current literature and guidelines.

METHODS

After the study was approved by the Ethics Committee on February 20, 2018 (Research Ethics Committee approval number: 2,501,524), questionnaires were sent to pediatric neurologists. We performed a cross-sectional study using a questionnaire based on literature and consisting of 28 multiple-choice questions covering the following topics related to ADHD: diagnosis,

pharmacological treatments, and non-pharmacological treatments for children with ADHD in the last 12 months of outpatient clinical care. A tool was used to guide the participants while filling out the questionnaire, making it impossible to move to the next page without properly filling out the current page, thereby preventing incomplete questionnaires.

The questionnaire was adapted to the Google Docs virtual platform and sent twice via e-mail and WhatsApp message to pediatric neurologists registered with the Brazilian Society of Pediatric Neurology. The time required to complete the questionnaire was approximately 10 minutes. No incentive was offered for participation and the questionnaire was only available in Brazilian Portuguese, the official language of Brazil.

The study included professionals who had completed their residency/specialization in pediatric neurology and clinical neurologists working in pediatric neurology. Specialists with laboratory conflicts of interest, professionals working as specialists for < 2 years, and professionals not working in Brazil were excluded.

The results obtained from the questionnaire were analyzed using descriptive statistics. In addition, the test of equality of proportions was used to compare two groups of pediatric neurologists (dichotomized according to the median time they worked as specialists), with a significance level of P = 0.05. In this test, the following variables were analyzed: request for evaluation and/or therapy with a multidisciplinary team (psychologists, psycho-pedagogists, speech therapists, occupational therapists); medical treatment in patients under 6 years of age (preschool age group), complementary tests before the beginning of treatment, option of performing continuous or intermittent treatment, and perception of symptomatic improvement in the face of the proposed treatment (medication with or without therapy with a multidisciplinary team).

RESULTS

Characterization of the participants

The data collection phase included 548 members of the Brazilian Society of Pediatric Neurology. Altogether, 788 invitations were sent including 548 by e-mail and 240 via messaging apps to reach 60 members with inactive and/or non-existent e-mails.

Altogether, 150 questionnaires were answered (27.4% of the 548 neuropediatricians). Twenty-two participants (14.7%) were excluded (20 participants worked as specialists for < 2 years, one participant incorrectly filled out the identification details and could not be confirmed by the Federal Council of Medicine, and one was a foreigner). Thus, 128 questionnaires were included in the study.

The participants' ages ranged from 29 to 74 years, with a mean age of 40.8 years (standard deviation [SD]: 8.9). The duration of working as a specialist ranged from 2 to 46 years, with a mean duration of 10.6 years (SD: 10.1) and a median duration of 6 years. Altogether, 106 participants (82.8%) reported part-time employment in the public health system (mainly responsible for attending to the low-income population in Brazil).

Diagnosis and treatment

All participants reported that they made the diagnosis of ADHD by anamnesis, endorsed by the clinical criteria in disease classification manuals. Seventy-one (71.1%) participants used the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) and 37 (28.9%) used the International Classification of Diseases-tenth edition (ICD-10). In addition, 122 (95.3%) reported using school reports; 114 (89.1%) used questionnaires such as the Swanson, Nolan, and Pelham-IV scale (SNAP IV); and 12 (9.4%) participants used other instruments.

Once the diagnosis was established, 123 (96.1%) participants reported referring the patient for assessment and/or treatment to a multidisciplinary team (psychologists, speech therapists, psycho-pedagogists, and occupational therapists). Among these professionals, most of the neurologists referred the patients to psychologists (n = 118, 95.9%).

A greater symptomatic improvement was perceived following combination treatment (combination of medication and intervention by a multidisciplinary team) when compared with other treatment schemes, with 124 (96.9%) of the participants reporting symptomatic improvement.

The use of medications was most frequent among patients aged 7–10 years (108 replies, 84.4%) when compared with those aged > 10 years and < 7 years, which corresponded to 15 (11.7%) and 5 (3.9%) replies, respectively. Short-acting methylphenidate was the most frequently prescribed medication (n = 109, 85.2%), followed by long-acting methylphenidate (n = 69, 53.9%) (**Table 1**).

Most of the participants (n = 65, 50.8%) indicated treatment for an indefinite duration with individualized management. When asked about continuous or intermittent use of medications in the last 12 months, 67 (52.3%) participants reported that they recommended pauses on weekends and/or during vacations, 27 (21.1%) recommended continuous treatment, and 34 (26.6%) recommended continuous use of medication as well as pauses on weekends and/or during vacations.

Table 1. Medications most commonly used by pediatric neurologists for attention deficit hyperactivity disorder

Medication	Number and percentage of the participants
Short-acting methylphenidate	109 (85.2%)
Long-acting methylphenidate	69 (53.9%)
Amphetamine	28 (21.9%)
Others (non-stimulants)*	43 (33.6%)

*Tricyclic antidepressants, bupropion, clonidine.

The most common side effect encountered by pediatric neurologists in clinical practice was headache, followed by hyporexia/lack of appetite, and weight loss (**Table 2**).

When asked about the need to discontinue or change the medications due to low tolerability, 111 (87%) participants answered in affirmative. However, 67 (60%) participants adopted this change in less than 10% of their patients.

With respect to complementary tests before starting the treatment, 94 (73.4%) participants requested laboratory tests, 91 (71.1%) requested an electrocardiogram, and 54 (42.2%) requested an electroencephalogram.

Statistical analysis between the groups according to the time they worked as specialists

Sixty-eight (53.1%) pediatric neurologists worked as specialists for ≤ 6 years, while 60 (49.9%) worked as specialists for > 6 years. Only one of the analyzed variables, namely "requesting a psychopedagogical evaluation" showed statistically significant difference between the groups.

DISCUSSION

The use of virtual environment has advantages as well as disadvantages for data collection. The advantages include the possibility of covering participants from different geographic locations, anonymity of participants, minimization of the researcher's influence, convenience of answering the instrument at the most appropriate time, ease of applying the instrument to several participants, obtaining large samples, minimizing typing errors once the data are entered into a virtual database, low cost, and possibility of mandatory filing of questions. The disadvantages include the possibility of e-mail being received by the participant as Sending and Posting Advertisement in Mass (SPAM), lack of skills of respondents, and dependence on technological resources and impersonality.[5,6,7] We obtained work responses from participants belonging to all Brazilian regions and all the questions were answered. However, 10.9% of the e-mails were sent to non-existent email addresses and we believe that others may have reached the participants as SPAM. We achieved a response rate of 27.4%, which is consistent with that reported in the literature (12–25% for virtual questionnaires).[5]

Table 2. Reported side effects of medications used for attention deficit hyperactivity disorder

Side effect	Number and percentage of the participants
Headache	99 (77.3%)
Weight loss	93 (72.6%)
Hyporexia/lack of appetite	93 (72.6%)
Anxiety	63 (49.2%)
Tic	52 (40.6%)
Insomnia	47 (36.7%)
Tachycardia	47 (36.7%)
Hyperexcitability	32 (25%)
Epileptic seizures	7 (5.5%)
Others*	14 (10.9 %)

*High blood pressure, mood changes, chest pain, psychotic symptoms, gastrointestinal tract symptoms.

All the interviewed specialists established the diagnosis of ADHD based on the criteria listed in classification systems such as DSM (71%) or ICD (28.9%).[1,8-10] A similar survey conducted by Fitzgerald and McNicholas[11] included 134 health professionals from seven European countries to evaluate topics such as attitudes, diagnosis, referral, treatment, and improvement in care. The responses showed similar distribution, with most of the participants (77%) using DSM as a diagnostic aid. These data highlight the importance of a solid base of updated diagnostic criteria and classification systems for mental disorders that are clinically eminent for diagnostic purposes. The preference for DSM suggests its greater clinical applicability with better characterization of symptoms compared to other classification systems, since it is a specific classification system for mental disorders. In contrast, although the version of ICD translated into Brazilian Portuguese covers all diseases, it does not contain the details of these diseases, as it is restricted to the classification of the diseases.[12,13]

Another aspect of these classification systems and diagnostic criteria is their impact on the variation in the prevalence of ADHD.[2] Consistency in the diagnosis was observed in the present series and all respondents reported that they based their diagnosis on the clinical history while following the current classification systems and using questionnaires or school reports. Other Brazilian authors[14,15] have observed similar results. Erbs[14] conducted a survey involving professionals working in the field of mental health (13 psychiatrists and one neurologist). This survey aimed to evaluate the diagnosis of ADHD in the city of Joinville (Santa Catarina, Brazil).[14] Peixoto and Rodrigues[15] evaluated the diagnosis and treatment of school children with ADHD by mental health professionals (ten psychiatrists and ten neurologists who worked in the city of Vitória, Espírito Santo, Brazil).[15] These authors evaluated the knowledge about ADHD among Brazilian health professionals and concluded that the diagnosis was mainly based on the DSM and/or ICD-10 diagnostic criteria.[14,15]

Pediatric neurologists in the present study uniformly understood the importance of a multidisciplinary team in the management of ADHD, with psychologists being the most commonly cited professionals. Similar results have been reported in the aforementioned surveys.[11,14,15] Evidence of the efficacy of behavioral therapy supports the role of psychologists in the treatment of ADHD.[3,16-20]

Most of the participants (n = 124, 96.9%) reported a significant improvement in symptoms following combination treatment.

Although initial results of the Multimodal Treatment of ADHD study emphasized the superiority of pharmacological treatment alone for symptomatic improvement, re-analyses and re-appraisals have highlighted the superiority of combination treatment for composite outcomes and for the domain of functional impairment.[21] However, respondents in the present survey reported symptomatic improvement following pharmacological treatment alone compared to exclusive psychotherapeutic intervention, highlighting the importance of pharmacological treatment for ADHD.[21, 22]

Analysis of the responses regarding indications of medication according to age group showed that the participants preferred pharmacological treatment for school-age children, which is consistent with the ADHD treatment guidelines that recommend the use of psychostimulants (first-line treatment) combined with behavioral interventions.[23,24]

Pharmacological treatment aims to normalize the prefrontal cortex activity by restoring the normal concentrations of dopamine and noradrenaline, which have been recognized to play a role in the physiopathology of ADHD. Thus, by strengthening the prefrontal cortical impulse, patients can recognize important stimuli and separate them from unnecessary ones, reducing hyperactivity and improving attention.[25-27] Psychostimulants are the first-choice drugs for the treatment of ADHD and are widely used in children aged > 6 years, adolescents, and adults with ADHD.[1,3,9,10,23-26]

Methylphenidate has been the most frequently prescribed psychostimulant for children and adolescents since the 1990s, accounting for 77 to 87% of all prescriptions for psychostimulants.[28] Methylphenidate was the most frequently indicated medication for the initial treatment of ADHD by the specialists in the present study. Short-acting methylphenidate was the most frequently prescribed medication, followed by long-acting methylphenidate and amphetamine. Similarly, short-acting methylphenidate was the most frequently prescribed medication by physicians in the survey conducted by Fitzgerald and McNicholas,[11] although its dosing convenience differs from that of long-acting methylphenidate, which can be administered in a single daily dose.[1,11,29-31] We believe that in addition to the possible benefits of short-acting medications such as a lower frequency of insomnia and weight loss, long-acting methylphenidate and amphetamines may eventually be prescribed less frequently, since they are more expensive and most of the respondents work at least part-time in the public health sector.[9,32-34] However, this issue as well as others that may interfere with the choice of medication (such as the patient's economic condition, presence of comorbidities at the time of ADHD diagnosis, and lack of response to psychostimulants) were not addressed in the present survey.

In contrast, 33.6% of participants reported the use of non-stimulant medications to treat ADHD. Approximately 30% of the children do not respond to or do not tolerate the initial stimulant and may benefit from medications such as tricyclic antidepressants, bupropion, clonidine, and atomoxetine (not commercialized in Brazil); which belong to drug classes other than methylphenidate or amphetamine.[35,36] These drugs were found to be efficacious in the treatment of ADHD, although with a lower therapeutic response than stimulants. In addition to their use as substitutes for stimulants, these medications may be used as adjuvants in the treatment of ADHD or even for the treatment of comorbidities.[1,9,10,31,37]

Almost half of the respondents indicated treatment for an indefinite period with individualized management. Together with the recognition that symptoms of ADHD persist throughout adulthood, stimulant medications can be continued throughout the life in most of the children diagnosed with ADHD during elementary school.[1,30] Discontinuation is indicated when the patient has been asymptomatic for approximately a year or when symptoms improve without the need for adjustments in medications. Development of side effects is another indication for discontinuing or reducing the dose of medications.[22,23,32]

The side effects of stimulants in children and adolescents are: uncommon, short-lived, and responsive to dose adjustments or tolerated with time of use (transient).[23] Severe side effects (movement disorders such as tics, obsessive-compulsive thoughts, psychotic symptoms) are rare and reversed by discontinuation of the medication.[9,23] Pediatric neurologists participating in this study reported headache as the most commonly encountered side effect in clinical practice, followed by hyporexia/lack of appetite and weight loss. Our findings were similar to those reported in a Brazilian study by Carlini et al.,[38] which was sponsored by a pharmaceutical company for the evaluation of main side effects of methylphenidate. Altogether, 7,500 questionnaires were sent to neurologists and psychiatrists and 892 (11.9%) questionnaires were answered. It is important to emphasize that we discussed the side effects of all medications used to treat ADHD, while the survey by Carlini et al.[38] evaluated the side effects of methylphenidate.

Possibly, the most frequently reported side effects are due to the use of short-acting methylphenidate, since it is the most frequently prescribed medication. We observed an agreement between the main side effects reported by the participants and those commonly described in clinical studies. In a randomized, double-blind, placebo-controlled trial, Greenhill et al.[39] found that among patients using methylphenidate, the most frequent side effect was headache, followed by lack of appetite, stomach pain, and insomnia.

There are guidelines for requesting complementary tests to monitor possible side effects. Some guidelines recommend obtaining a detailed clinical history including personal or family history of cardiovascular diseases, presence of tics, and sleep disorders (insomnia) before starting pharmacological treatment for ADHD; since these conditions can be aggravated by

the treatment for ADHD, especially when psychostimulants are used.[40,41] During physical examination before starting the medication, it is important to measure weight, height, blood pressure, and heart rate to determine the exact time of occurrence of the main side effects and to carry out the correct management as previously described.[9,40,41] Ninety-four (73.4%) participants in the present study reported requesting laboratory tests and 91 (71.1%) requested an electrocardiogram. According to Cortese et al.,[32] there is no evidence suggesting that pharmacological treatment with psychostimulants is associated with alterations in the QT interval, sudden cardiac death, acute myocardial infarction, or cerebrovascular accidents. Some of the main guidelines for the treatment of ADHD (American Academy of Pediatrics, Canadian ADHD Practice Guidelines, National Institute for Health and Clinical Excellence Guideline) and some systematic reviews do not recommend a routine electrocardiogram. It is indicated only in case of family and/or personal history of cardiovascular diseases, a history of sudden death among first-degree relatives, risk of QT-interval alteration by the medication of choice, and changes in cardiac physical examination.[40-45] Since the participants were not asked about the reason for requesting the exam, we believe that some requests for complementary electrocardiograms were due to a family or personal history of heart diseases.

Fifty-four (42.2%) specialists reported requesting an electroencephalogram before starting the treatment. These participants believed that psychostimulants may reduce the seizure threshold. According to Kaufmann et al.,[46] methylphenidate, the main psychostimulant used to treat ADHD, can cause sleep deprivation and reduce the seizure threshold. However, it does not exert any effect on neurotransmitters such as gamma-aminobutyric acid, glutamate, and aspartate or on calcium and sodium, which are associated with the physiopathology of epilepsy. These findings suggest that methylphenidate does not increase the risk of epileptic seizures.[46] Controlled clinical trials have demonstrated the safety and efficacy of methylphenidate in children with both epilepsy and ADHD.[33,47-50] These studies have concluded that methylphenidate can be used safely in patients with ADHD without epilepsy, with controlled epileptic seizures, or with electrographic alterations in the absence of clinical seizures. In patients with uncontrolled epileptic seizures, careful clinical follow-up and electrographic monitoring are necessary during treatment.[50]

The last debatable point in the management of patients was continuity of treatment. Considering the heterogeneity of the disorder, we found different management practices among our participants regarding the indication of continuous use of psychostimulants or pausing on weekends and/or during school vacations. Pausing the medication is generally indicated when the symptoms compromise school performance due to side effects such as insomnia, lack of appetite, weight loss, and growth retardation.[1,9,22,23,32]

The two groups of specialists exhibited similar behavior regarding requests for evaluation and therapy by a multidisciplinary team. However, request for psycho-pedagogical evaluation was more frequent among pediatric neurologists who worked as specialists for ≤ 6 years, which could be attributed to concomitant learning disabilities at the time of ADHD diagnosis (a prevalence of 10 to 25%).[51,52]

Limitations

It was not possible to accurately determine the response rate. Hence, we could not extrapolate these behaviors to all Brazilian pediatric neurologists due to methodological limitations.

CONCLUSION

The present study evaluated aspects of ADHD considered important by researchers. These included diagnostic resources as well as questions regarding treatment such as the role of a multidisciplinary team, most suitable drugs, reasons for discontinuing treatment, most common side effects, requests for complementary tests before starting the medications, and continuity of treatment. Brazilian pediatric neurologists participating in this study complied with clinical guidelines as well as guidelines regarding pharmacological and non-pharmacological treatments, emphasizing the importance of diagnostic manuals and treatment guidelines for an eminently clinical situation and enabling uniformity in quality treatment.

REFERENCES

1. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020. PMID: 27189265; https://doi.org/10.1038/nrdp.2015.20.
2. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942-8. PMID: 17541055; https://doi.org/10.1176/ajp.2007.164.6.942.
3. Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. N Engl J Med. 2014;370(9):838-46. Erratum in: N Engl J Med. 2015;372(2):197. Dosage error in text. PMID: 24571756; https://doi.org/10.1056/NEJMcp1307215.
4. Centers for Disease Control and Prevention. Children's Mental Health. Data & Statistics. Available from: https://www.cdc.gov/childrensmentalhealth/data.html. Accessed in 2022 (Sep 28).
5. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev. 2009;2009(3):MR000008. PMID: 19588449; https://doi.org/10.1002/14651858.MR000008.pub4.
6. Fleming CM, Bowden M. Web-based surveys as an alternative to traditional mail methods. J Environ Manage. 2009;90(1):284-92. PMID: 18082316; https://doi.org/10.1016/j.jenvman.2007.09.011.

7. van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? Am J Epidemiol. 2010;172(11):1292-8. PMID: 20880962; https://doi.org/10.1093/aje/kwq291.
8. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. Cleve Clin J Med. 2015;82(11 Suppl 1):S2-7. PMID: 26555810; https://doi.org/10.3949/ccjm.82.s1.01.
9. Moriyama TS, Cho AJM, Verin RE, et al. Attention deficit hyperactivity disorder. In: Rey JM, Zepf FD, editors. IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2012. p. 1-23.
10. Rohde LA, Buitelaar JK, Gerlach M, Faraone SV. The World Federation of ADHD Guide. Porto Alegre: Artmed; 2019. Available from: http://www.russellbarkley.org/factsheets/TheWorldFederationOfAdhdGuide.pdf. Accessed in 2022 (Sep 28).
11. Fitzgerald M, McNicholas F. Attitudes and practices in the management of ADHD among healthcare professionals who responded to a European survey. Ir J Psychol Med. 2014;31(1):31-7. PMID: 30189470; https://doi.org/10.1017/ipm.2013.45.
12. American Psychiatric Association. DSM-5 Task Force. 5th ed. Washington, DC: American Psychiatric Publishing; 2013. https://doi.org/10.1176/appi.books.9780890425596.
13. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993. Available from: https://apps.who.int/iris/handle/10665/37108.
14. Erbs GC. As várias formas de avaliação do TDAH na cidade de Joinville. Psicologia.pt. 2010. Available from: https://www.psicologia.pt/artigos/ver_artigo.php?codigo=A0540. Accessed in 2022 (Sep 28).
15. Peixoto ALB, Rodrigues MMP. Diagnóstico e tratamento de TDAH em crianças escolares, segundo profissionais da saúde mental. Aletheia. 2008;28:91-103. Available from: http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S1413-03942008000200008&lng=pt. Accessed in 2022 (Sep 28).
16. Antshel KM, Olszewski AK. Cognitive behavioral therapy for adolescents with ADHD. Child Adolesc Psychiatr Clin N Am. 2014;23(4):825-42. PMID: 25220089; https://doi.org/10.1016/j.chc.2014.05.001.
17. Evans SW, Owens JS, Wymbs BT, Ray AR. Evidence-Based Psychosocial Treatments for Children and Adolescents With Attention Deficit/Hyperactivity Disorder. J Clin Child Adolesc Psychol. 2018;47(2):157-98. PMID: 29257898; https://doi.org/10.1080/15374416.2017.1390757.
18. Ferrin M, Sonuga-Barke E, Daley D, et al. Non-pharmacologic treatments for attention-deficit/hyperactivity disorder (ADHD). In: Rey JM, editor. IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2016. p. 1-23. Available from: https://iacapap.org/_Resources/Persistent/59eb6381de4a279b84838d2fc367fe701b0c50ea/D.1.1-ADHD-NON-PHARMA-2016.pdf. Accessed in 2022 (Sep 28).
19. He JA, Antshel KM. Cognitive behavioral therapy for attention-deficit/hyperactivity disorder in college students: a review of the literature. Cognitive and Behavioral Practice. 2017;24(2):152-73. https://doi.org/10.1016/j.cbpra.2016.03.010.
20. Knouse LE, Safren SA. Current status of cognitive behavioral therapy for adult attention-deficit hyperactivity disorder. Psychiatr Clin North Am. 2010;33(3):497-509. PMID: 20599129; https://doi.org/10.1016/j.psc.2010.04.001.
21. Hinshaw SP, Arnold LE; For the MTA Cooperative Group. ADHD, Multimodal Treatment, and Longitudinal Outcome: Evidence, Paradox, and Challenge. Wiley Interdiscip Rev Cogn Sci. 2015;6(1):39-52. PMID: 25558298; https://doi.org/10.1002/wcs.1324.
22. Rohde LA, Halpern R. Transtorno de déficit de atenção/hiperatividade: atualização [Recent advances on attention deficit/hyperactivity disorder]. J Pediatr (Rio J). 2004;80(2 Suppl):S61-70. PMID: 15154074; https://doi.org/10.2223/1170.
23. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(7):894-921. PMID: 17581453; https://doi.org/10.1097/chi.0b013e318054e724.
24. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528. Erratum in: Pediatrics. 2020;145(3). PMID: 31570648; https://doi.org/10.1542/peds.2019-2528.
25. Bidwell LC, McClernon FJ, Kollins SH. Cognitive enhancers for the treatment of ADHD. Pharmacol Biochem Behav. 2011;99(2):262-74. PMID: 21596055; https://doi.org/10.1016/j.pbb.2011.05.002.
26. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother. 2014;48(2):209-25. PMID: 24259638; https://doi.org/10.1177/1060028013510699.
27. Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009;57(7-8):579-89. PMID: 19627998; https://doi.org/10.1016/j.neuropharm.2009.07.026.
28. Zito JM, Safer DJ, DosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. Arch Pediatr Adolesc Med. 2003;157(1):17-25. PMID: 12517190; https://doi.org/10.1001/archpedi.157.1.17.
29. Coghill D, Banaschewski T, Zuddas A, et al. Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies. BMC Psychiatry. 2013;13:237. Erratum in: BMC Psychiatry. 2015;15:202. PMID: 24074240; https://doi.org/10.1186/1471-244X-13-237.
30. Connor DF, Steingard RJ. New formulations of stimulants for attention-deficit hyperactivity disorder: therapeutic potential. CNS Drugs. 2004;18(14):1011-30. PMID: 15584770; https://doi.org/10.2165/00023210-200418140-00005.
31. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother. 2014;48(2):209-25. PMID: 24259638; https://doi.org/10.1177/1060028013510699.

32. Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry. 2013;54(3):227-246. PMID: 23294014; https://doi.org/10.1111/jcpp.12036.
33. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs. 2008;22(3):213-37. PMID: 18278977; https://doi.org/10.2165/00023210-200822030-00003.
34. Pastura G, Mattos P. Efeitos colaterais do metilfenidato. Arch Clin Psychiatry (São Paulo). 2004;31(2):100-4. https://doi.org/10.1590/s0101-60832004000200006.
35. Spencer T, Biederman J, Wilens T. Nonstimulant treatment of adult attention-deficit/hyperactivity disorder. Psychiatr Clin North Am. 2004;27(2):373-83. PMID: 15064003; https://doi.org/10.1016/j.psc.2003.12.001.
36. Waxmonsky JG. Nonstimulant therapies for attention-deficit hyperactivity disorder (ADHD) in children and adults. Essent Psychopharmacol. 2005;6(5):262-76. PMID: 16222911.
37. Dopheide JA, Pliszka SR. Attention-deficit-hyperactivity disorder: an update. Pharmacotherapy. 2009;29(6):656-79. PMID: 19476419; https://doi.org/10.1592/phco.29.6.656.
38. Carlini A, Nappo AS, Nogueira V, Naylor FGM. Metilfenidato: Influência da Notificação de Receita A (cor amarela) sobre a prática de prescrição por médicos brasileiros. Arch. Clin. Psychiatry (São Paulo). 2003;30(1):11-20. https://doi.org/10.1590/S0101-60832003000100002.
39. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-93. Erratum in: J Am Acad Child Adolesc Psychiatry. 2007;46(1):141. PMID: 17023867; https://doi.org/10.1097/01.chi.0000235077.32661.61.
40. Canadian ADHD Resource Alliance (CADDRA): Canadian ADHD Practice Guidelines. Fourth Edition. Toronto ON: CADDRA; 2018.
41. NICE - National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: diagnosis and management. Nice Guideline nº 87. March, 2018. Available from: https://www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933. Accessed in 2022 (Sep 28).
42. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528. Erratum in: Pediatrics. 2020;145(3). PMID: 31570648; https://doi.org/10.1542/peds.2019-2528.
43. Aggarwal V, Aggarwal A, Khan D. Electrocardiogram before starting stimulant medications: to order or not? Cardiol Young. 2016;26(1):216-9. PMID: 26278960; https://doi.org/10.1017/S1047951115001274.
44. Elia J, Vetter VL. Cardiovascular effects of medications for the treatment of attention-deficit hyperactivity disorder: what is known and how should it influence prescribing in children? Paediatr Drugs. 2010;12(3):165-75. PMID: 20481646; https://doi.org/10.2165/11532570-000000000-00000.
45. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240-50. PMID: 26386541; https://doi.org/10.1016/S0140-6736(15)00238-X.
46. Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. J Child Neurol. 2009;24(6):727-33. PMID: 19491115; https://doi.org/10.1177/0883073808330165.
47. Gonzalez-Heydrich J, Dodds A, Whitney J, et al. Psychiatric disorders and behavioral characteristics of pediatric patients with both epilepsy and attention-deficit hyperactivity disorder. Epilepsy Behav. 2007;10(3):384-8. PMID: 17368109; https://doi.org/10.1016/j.yebeh.2007.01.010.
48. Gucuyener K, Erdemoglu AK, Senol S, et al. Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. J Child Neurol. 2003;18(2):109-12. PMID: 12693777; https://doi.org/10.1177/08830738030180020601.
49. Gross-Tsur V, Manor O, van der Meere J, Joseph A, Shalev RS. Epilepsy and attention deficit hyperactivity disorder: is methylphenidate safe and effective? J Pediatr. 1997;130(1):40-4. Corrected and republished in: J Pediatr. 1997;130(4):670-4. PMID: 9003849; https://doi.org/10.1016/s0022-3476(97)70308-1.
50. Hemmer SA, Pasternak JF, Zecker SG, Trommer BL. Stimulant therapy and seizure risk in children with ADHD. Pediatr Neurol. 2001;24(2):99-102. PMID: 11275457; https://doi.org/10.1016/s0887-8994(00)00240-x.
51. Rotta NT, Ohlweiler L, Riesgo RS. Transtornos da aprendizagem. abordagem neurobiológica e multidisciplinar. Porto Alegre: Editora Artmed; 2016. p. 262-356, 392-405.
52. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. 1997;36(10 Suppl):85S-121S. PMID: 9334567; https://doi.org/10.1097/00004583-199710001-00007.

Authors' contributions: Nunes MES: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal), writing-review, and editing (equal); Zuanetti PA: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal), writing-review, and editing (equal); Hamad APA: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources

(equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal), writing-review, and editing (equal). All authors actively contributed to the discussion regarding the study results and reviewed and approved the final version for publication

Acknowledgments: The authors would like to thank the pediatric neurologists for their participation, without whom this study would not have been possible

Sources of funding: There are no funding sources to report
Conflicts of interest: None

Date of first submission: December 5, 2021
Last received: April 22, 2022
Accepted: September 20, 2022

Address for correspondence:
Marina Estima Neiva Nunes
Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP)
Av. Bandeirantes, 3.900
Monte Alegre — Ribeirão Preto (SP) — Brasil
CEP 14049-900
Tel. (+55 16) 3963-6668/3963-6669
E-mail: marinapesquisatdah@gmail.com

INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal accepts manuscripts previously deposited in a trusted preprint server.

São Paulo Medical Journal supports Open Science practices. It invites reviewers to join Open Peer Review practices through acceptance that their identities can be revealed to the authors of articles. However, this is purely an invitation: reviewers may also continue to provide their input anonymously.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal applies a publication fee in the form of an article processing charge (APC) for all studies conducted outside of Brazil. This rate will be charged to the corresponding author when the study has been accepted on the grounds of its scientific merit. This fee is US$ 500.00 and is independent of the length of the text. The corresponding author should wait to receive the journal's invoice before making the payment. The article will only be published after presentation of the proof of payment. Submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific 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] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends 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. The existence and declaration of conflicts of interest is not an impediment to publication at all.

Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

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* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

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 regarding format. 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 promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript 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 the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's 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.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least 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 is not under consideration by 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 the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text 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. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

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 are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

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.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, 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. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

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. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, 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.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

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 should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
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, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. 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"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English 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.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

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 are only available electronically.

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.

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.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

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. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

DOCUMENTS CITED

1. Internal Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available from: http://www.icmje.org/recommendations/. Accessed in 2019 (March 11).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/. Accessed in 2018 (May 3).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Br J Surg 2002. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2168.2000.01610.x. Accessed in 2019 (April 4).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: www.prisma-statement.org. Accessed in 2019 (April 4).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2018 (May 3).
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. PMID: 18313558. doi: 10.1016/j.jclinepi.2007.11.008.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: https://www.equator-network.org/reporting-guidelines/care/. Accessed in 2018 (May 3).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.equator-network.org/reporting-guidelines/stard/. Accessed in 2018 (May 3).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90. doi:10.1001/jama.289.1.89.
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 2019 (March 11).
11. International Committee of Medical Journal Editors. Overlapping Publications. Available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html. Accessed in 2018 (Feb 18).
12. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed in 2018 (May 3).
13. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687. PMID: 24609605; doi: 10.1136/bmj.g1687.
14. Non-randomised controlled study (NRS) designs. Available from: http://childhoodcancer.cochrane.org/non-randomised-controlled-study-nrs-designs. Accessed in 2018 (May 3).

III CONGRESSO
PAULISTA DE DOR 2023

28 a 30 setembro

VENHA SE ATUALIZAR NO DIAGNÓSTICO E TRATAMENTO DA DOR NAS DIVERSAS ESPECIALIDADES

Chegamos a terceira edição do Congresso Paulista de Dor, desta vez totalmente presencial e com muitas novidades, como as oficinas "A dor de Ouvir a Dor" e um módulo de introdução aos conceitos básicos de dor para alunos de medicina e residentes.

CONFIRA ALGUNS TEMAS

- Anestesiologia;
- Fisiatria;
- Termografia;
- Medicina Aeroespacial;
- Medicina do Esporte;
- Psiquiatria & Dor;
- Oficinas Dor de Ouvir a Dor;
- Ortopedia;
- Cefaleia;
- Sono;
- Neurologia;
- Cannabis;
- Geriatria;
- Endocrinologia;
- Acupuntura;
- Reumatologia.

GARANTA SEU LUGAR!

VAGAS LIMITADAS

Local do evento: Associação Paulista de Medicina
Av. Brigadeiro Luís Antônio, 278 - Bela Vista,
São Paulo - SP | CEP: 01318-901

Médico Técnico Científico responsável pelo evento:
Dra. Telma Regina Mariotto Zakka / CRM 33741 SP

Realização e comercialização: APM Associação Paulista de Medicina

Apoiador Institucional: SBOT Sociedade Brasileira de Ortopedia e Traumatologia

Patrocinador Master: ENDOGEN Ciência para vida

Na Quali, sua saúde tem escolha.

SulAmérica Saúde

amil

Unimed Nacional

SEGUROS Unimed

São Cristóvão saúde

Simule seu plano

ou ligue
(11) 31884200

*Condições no site.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

quali corp

SulAmérica: ANS nº 005622
Amil: ANS nº 326305
Central Nacional Unimed: ANS nº 339679
Unimed Seguros: ANS nº 00.070-1
São Cristóvão Saúde: ANS nº 314218
Qualicorp Adm. de Benefícios: ANS nº 417173