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Transplantation Beyond Species: The Present and Future of Xenotransplantation

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Xenotransplantation (XTx), the transplantation of organs, tissues, or cells from animals to humans, is emerging as a promising alternative to address the increasing global demand for transplantable organs. Over the past two decades, substantial progress has been made in transplantation practices worldwide, driven by advancements in healthcare infrastructure and the expansion of organ donation programs involving both living and deceased donors. Global data show a significant rise in transplant activity in regions such as the United States, Europe, China, and India, emphasizing a broader international effort to address organ shortages. Despite global advances in transplantation, considerable disparities in access persist, particularly in low- and middle-income countries, where limited infrastructure and socioeconomic inequalities continue to impede equitable care. Consequently, millions of patients continue to face barriers to life-saving transplants, highlighting the urgent need for international collaboration and strategic investments to expand access.

Brazil is recognized for maintaining one of the largest public transplant systems in the world. From preoperative preparation to lifelong posttransplant pharmacotherapy, transplantation constitutes one of the most resource-intensive interventions funded by the Unified Health System (*Sistema Único de Saúde*), which accounts for approximately 96% of all heart transplants performed in Brazil.[1]

Despite significant advances in transplant techniques and public policies, the supply of organs still fails to meet the growing demand, resulting in increasingly long waiting lists, as evidenced by the Brazilian Transplant Registry.[2] This scenario underscores the urgent need to guarantee fair access to transplantation, as established by the 1988 Federal Constitution and Law No. 8,080/1990,[3] which defines health as a right of all and a duty of the State. In the context of a shortage of human organs and increasing demand for new therapeutic alternatives, XTx has emerged as a promising and potentially viable solution.

The history of XTx closely follows the overall development of transplantation. The earliest reports of such procedures involve tissue and cell transplants, rather than organ transplants.[4] Initial experiments date back to the 17th century, most notably the xenotransfusions conducted by Jean-Baptiste Denis in 1667 using the blood of a lamb.[5] Another significant milestone occurred in 1838, when Richard Sharp Kissam performed the first corneal XTx by transplanting porcine corneal tissue into a human patient.[6] Throughout the 19th and 20th centuries, advances in vascular anastomosis techniques—pioneered by Mathieu Jaboulay and Alexis Carrel—enabled a series of experimental attempts that involved organs from several species, including nonhuman primates (NHP; baboons and chimpanzees), pigs, rabbits, and sheep. However, these experiments were largely unsuccessful, primarily due to the occurrence of hyperacute rejection and other severe immunological complications.[4,7]

The advent of modern immunosuppression in the 1960s, fueled by the discoveries of Peter Medawar and the introduction of drugs such as 6-mercaptopurine, marked a new era, enabling significant progress in both allotransplantation and XTx.[4] From that point forward, the first clinical reports of cardiac XTx in humans began to emerge. Among the key milestones: 1964 – chimpanzee heart, by James Hardy, in Jackson (USA), with a survival time of 90 min;[8] 1968 – porcine heart, by Donald Ross, in London (UK), with a survival time of 4 min;[9] 1968 – sheep heart, by

Denton Cooley, in Austin (USA), with a survival time of 10 min;[10] 1969 – chimpanzee heart, by Marion, in Lyon (France), with immediate death;[11] 1977 – baboon heart (patient 1) and chimpanzee heart (patient 2), by Christiaan Barnard, in Cape Town (South Africa), with survival times of 5.5 h and 4 days, respectively;[12] 1984 – baboon heart, in the iconic "Baby Fae" case, by Leonard Bailey, in Loma Linda (USA), with a survival time of 20 days;[13] 1992 – porcine heart, by Zbigniew Religa, in Sosnowiec (Poland), with a survival time of 23 h;[14] and 1996 – porcine heart, by Dhani Ram Baruah, in Sonapur (India), with a survival time of 7 days.[15] Notably, no lung XTx has ever been performed.

The main barrier—hyperacute rejection—remained insurmountable, resulting in survival times ranging from several minutes to a few days. During the 1990s, research progressed toward a more comprehensive understanding of the innate and adaptive immune systems, complement cascade, coagulation pathophysiology, and inflammatory responses.[7]

Due to the unsuccessful use of NHP hearts for cardiac transplantation, pigs emerged as the most promising donor species for several reasons: their hearts closely resemble human hearts in size and anatomy; their genetic similarities to humans facilitate precise genetic modifications; they have favorable reproductive characteristics and husbandry practices; they pose a lower relative risk of infections; and, from an ethical and moral standpoint, their use is generally considered more acceptable than that of NHPs. However, due to significant evolutionary differences between pigs and primates, porcine organs transplanted into NHPs and humans undergo hyperacute rejection. A key factor in such rejection is the presence, in humans, of naturally occurring preformed antibodies against carbohydrate antigens expressed on the surface of porcine cells.[16,17]

A major breakthrough in preventing hyperacute rejection was identifying the carbohydrate alpha-galactose-1,3-galactose linkage as the main xenoepitope responsible for triggering this immune response. After this discovery, genetically modified pigs lacking the gene for the enzyme alpha-1,3-galactosyltransferase were created, leading to the first successful experiments and opening a new chapter for XTx using genetically modified pigs.[16]

The deletion of porcine genes related to immune regulation and thrombosis pathways led to further advancements in the field of XTx. In 2012, the introduction of the CRISPR/Cas9 gene-editing tool further facilitated the development of safer porcine donor lines by enabling the removal of porcine endogenous retroviruses.[18]

On January 7, 2022, a genetically modified porcine heart, developed by United Therapeutics, was successfully transplanted into a 57-year-old patient with end-stage heart failure at the University of Maryland Medical Center, United States. The patient had been deemed ineligible for conventional advanced heart failure therapies. The patient died on March 8, 2022.[4]

While early clinical initiatives beginning in the 1960s focused on heart transplantation, renal XTx has progressively gained broader acceptance, with accumulating clinical experience. This shift in preference is due to the technical challenges associated with cardiac transplantation using genetically modified porcine hearts, which contrasts with the following factors favoring renal XTx: (1) greater tolerance of the kidneys to temporary dysfunction (functional resilience);[19] (2) anatomical and physiological compatibility of porcine kidneys with human systems;[20] (3) lower immediate clinical impact of graft failure,[21] including greater ease in removing the transplanted organ (graft nephrectomy); (4) a broader and more accumulated knowledge of renal immunology from preclinical models since the 1990s, particularly studies including porcine kidneys implanted into NHP, as well as the development of immunosuppressive therapies more precisely tailored to the renal environment;[18] and achieved (5) faster progress in genetic modifications targeting kidney function. For example, deleting genes such as GGTA1, CMAH, and B4GALNT2, along with adding human genes like CD46, thrombomodulin, and CD47, has enhanced immunologic and functional performance, especially in the kidneys, leading to promising and potentially transformative clinical outcomes in humans.19 Therefore, choosing the kidney as the first solid organ for clinical XTx trials results from a combination of clinical, immunological, and operational factors that make it safer and more predictable for trials than vital organs lacking effective artificial support.19,20 This decision improves ethical and regulatory acceptability while enabling gradual and sustainable progress in the field of clinical XTx. In Brazil, promising initiatives are being led by experienced research groups, notably including renowned professionals such as Silvano Raia, Mayana Zatz, Rodrigo Vianna, and Jorge Kalil. The Brazilian project aims to establish a robust XTx platform, integrating sequential phases including advanced genetic engineering, embryo fertilization and cloning, management and development of genetically modified pigs, preclinical evaluations, and experiments involving brain-dead human subjects, culminating in clinical trials projected to begin in 2027. The goal is to obtain regulatory approval from the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária*) by 2029.

Central aspects of the project include technical and scientific advances, as well as a strong focus on infrastructure dedicated to animal welfare. Strict protocols follow the standards established by the National Council for the Control of Animal Experimentation (*Conselho Nacional de Controle de Experimentação Animal*), with specialized animal care aimed at minimizing suffering and guaranteeing the highest health standards for the animals involved.

From an ethical and bioethical standpoint, XTx raises complex issues ranging from patient autonomy to clear criteria for candidate selection for the procedure. The importance of developing detailed and transparent informed consent forms, as well as guaranteeing

justice and equity in access to XTx for all patients across both the public and private healthcare systems, remains a constant concern.

In the global context, the World Health Organization recommends the establishment of national regulatory bodies specifically dedicated to supervising XTx activities. These institutions must guarantee that all procedures are conducted in accordance with the highest ethical and safety standards.

The potential for clinical trials including solid organ XTx has been a topic of extensive debate. The cardiac xenotransplants performed in living human recipients at the University of Maryland sparked debate over the feasibility of initiating clinical trials for cardiac XTx. Several countries are currently deliberating whether—and how—to move forward with such trials. One example is the recent creation of the Medical Porcine Development Association in Japan, which reflects the growing interest of the local scientific community in XTx. The association aims to develop new medical care protocols and improve technologies for producing pigs intended for clinical use.[22] In China, a major milestone was achieved with the first clinical liver XTx: a genetically modified auxiliary porcine liver was transplanted into a 71-year-old living patient as an approach to avoid small-for-size syndrome following extensive resection for hepatocellular carcinoma.[23]

The field of XTx offers opportunities that extend beyond whole-organ replacement, with several interspecies applications already demonstrating promising clinical results. A notable example is implanting dopamine-producing cells derived from pigs into the substantia nigra of patients with Parkinson's disease, with the goal of functional cell replacement. Additionally, the effectiveness of xenografts has been proven in various therapeutic settings, such as using porcine skin for temporary wound coverage, corneal transplantation to restore vision, and implanting porcine pancreatic islets as an experimental treatment for diabetes mellitus.4 Although further studies and regulatory discussions on clinical trials involving solid organ XTx are still needed, the procedures already being performed in living human recipients worldwide have increased global interest and scrutiny. XTx has become a realistic and promising treatment option, as long as it is conducted with scientific integrity, ethical responsibility, and strict regulatory oversight, always prioritizing human well-being and animal welfare.

As Elmi Muller emphasized in her opening address at the 30th International Congress of The Transplantation Society (Istanbul, September 2024): "The future of transplantation depends not just on innovation but also on our commitment to ensuring that advancements reach all corners of the globe—ethically, sustainably, and equitably. Together, let us commit to a future where transplantation is not a privilege but a fundamental right—accessible, safe, and sustainable for all."[24]

This perspective reinforces the need to prioritize XTx within the national research agenda in Brazil, including both basic and clinical sciences.

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Functional Index Questionnaire: structural validity study in Brazilian patients with anterior knee pain

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ABSTRACT

OBJECTIVE: To assess the Functional Index Questionnaire (FIQ) structure using confirmatory factor analysis (CFA) in Brazilian patients with anterior knee pain.

METHODS: Brazilian patients of both sexes (n = 100), aged ≥ 18 years, with anterior knee pain for at least 3 months were included. Eligible participants completed an online form that collected personal and clinical data as well as responses to the assessment tools. We used CFA and the following fit indices: chi-square/degrees of freedom (DF), comparative fit index (CFI), Tucker–Lewis index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residuals (SRMR).

RESULTS: The majority of the respondents were women, young adults, overweight, with incomplete higher education, were physically active, and had pain in sitting or squatting positions. The mean duration of pain was 38.24 months, and the mean pain intensity was 4.54 points. The model fit indices were as follows: χ^2/DF = 2.08, TLI = 0.978, CFI = 0.969, RMSEA = 0.104, and SRMR = 0.077. Therefore, the one-dimensional structure with eight items yielded an RMSEA value above the 0.08 cutoff point, suggesting a poorer fit and more residual error than is acceptable for a well-fitting model. Using the modification indices within the CFA, we observed a correlation between Items 2 (climbing up two flights of stairs [16 steps]) and 6 (climbing up four flights of stairs [32 steps]) and Items 3 (squatting) and 4 (kneeling), indicating the similarity in the response pattern for these items. After adding these correlations to the model, we obtained improved fit indices (χ^2/DF = 1.51, TLI = 0.990, CFI = 0.985, RMSEA = 0.072, and SRMR = 0.061).

CONCLUSION: This version of the FIQ should be used with caution, as the unidimensional model demonstrates substantial residuals, mainly because of item redundancy.

INTRODUCTION

The use of patient-reported outcome measures to assess anterior knee pain is recommended.[1,2] Consequently, several clinical assessment instruments have been reported in the literature.[3–6] The Functional Index Questionnaire (FIQ) is a widely used outcome measure for assessing functional limitations in patients with anterior knee pain.[3–6] This instrument was first developed by Stratford and Heuff[6] and subsequently validated by Chesworth et al.[5] It is easy to administer, and its reliability and validity have been documented in patients with anterior knee pain. Moreover, patients with anterior knee pain haven chosen the FIQ as the easiest questionnaire to complete among other outcome measures.[1]

Currently, the FIQ has been cross-culturally adapted and translated into Persian[4] and Brazilian Portuguese.[3] Negahban et al.[4] examined test-retest reliability, internal consistency, construct validity, and factor analysis to determine the number of underlying factors and the items that load on each factor. Cunha et al.[3] tested the internal consistency, ceiling and floor effects, construct validity, reproducibility, and responsiveness. However, the Brazilian version of the FIQ[3] did not assess the internal structure of the FIQ as recommended in the guidelines.[7]

Therefore, this study aimed to assess the structure of the FIQ using confirmatory factor analysis (CFA) in Brazilian patients with anterior knee pain. We hypothesized that the unidimensional 8-item model of the FIQ would demonstrate adequate fit.

METHODS

Study design and recruitment

This study has a cross-sectional design and investigated the structural validity of the FIQ.[3] Data collection for the study was conducted using an online form (Google Forms, Mountain View,

California) in rehabilitation clinics and gyms in São Luís, northeast of Brazil.

This study was approved by the Research Ethics Committee of the Universidade Federal do Maranhão (report number 3.995.226), and the guidelines were in accordance with the Declaration of Helsinki (i.e., all experiments were performed in accordance with the relevant guidelines and regulations). All respondents freely participated in the study and signed an informed consent form.

Sample size and eligibility

The minimum sample size considered in this study was 100 participants, as recommended by the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN).[7] We included participants of both sexes, sedentary or active, between the ages of 18 and 60 years, who reported anterior knee pain for at least 3 months.[8] We adopted the following exclusion criteria: history of trauma, fracture, or acute injury to the knee joint; knee surgery; use of analgesics in the past seven days; physiotherapy treatment for anterior knee pain in the past 3 months; and presence of other chronic pain.[9]

Evaluation tools

We used the numerical pain rating scale (NPRS) to characterize participants' pain intensity.[10] It is a unidimensional scale from 0 to 10 points, where 0 is "no pain" and 10 is the "worst pain imaginable" with adequate validity for Brazilians.[10] In addition to the NPRS and an initial assessment (covering personal and anthropometric characteristics of the sample), we applied the FIQ, a scale adapted for Brazilian Portuguese[3] with eight items and three response options for each item ("unable to do" = 0 points, "can do with a problem" = 1 point, and "no difficulty" = 2 points). The total score ranges from 0 ("complete inability to perform everyday life activities") to 16 ("no problems performing everyday life activities").

Statistical analysis

We performed a descriptive analysis and presented the data as means and standard deviations, or as relative and absolute frequencies. We used CFA to identify the best structure of the FIQ using R Studio (Boston) and the lavaan and semPlot packages. A polychoric matrix and robust diagonally weighted least-squares (RDWLS) extraction method were applied.[11,12]

We considered adequate values of fit indices for the following cutoff values: χ^2/degree of freedom (DF) < 3; comparative fit index (CFI) and Tucker–Lewis index (TLI) > 0.90; and root mean square error of approximation (RMSEA) and standardized root mean square residuals (SRMR) < 0.08.[13,14] Factor loadings were considered adequate when >0.40,[15] and we used the modification indices to identify redundancy or discrepancies in the model.

RESULTS

A total of 100 participants participated in this study. Among them, 65% were young women (31.76 [12.28]), overweight (body mass index > 25 kg/m²), incomplete higher education (38%), and physical activity practitioners (64.4%) (**Table 1**). We observed that most participants presented with pain in the sitting (82%) or squatting (67%) positions, with a mean pain duration of 38.24 months and a mean pain intensity of 4.54 points. A similar distribution of unilateral pain was observed on the right (33%), left (36%), and bilateral (31%) sides (**Table 2**).

Table 1. Personal and anthropometric characteristics of the sample (n = 100)

Characteristics	Mean (standard deviation) or %
Age (years)	31.76 (12.28)
Body mass (kg)	71.15 (15.24)
Stature (m)	1.65 (0.08)
Body mass index (kg/m²)	25.79 (4.39)
Sex	
Male	65%
Female	35%
Education	
Incomplete primary education	1%
Primary education	1%
Incomplete secondary education	1%
Secondary education	12%
Incomplete graduate	38%
Graduate	26%
Incomplete postgraduate	5%
Postgraduate	16%
Lower limb dominance	
Right	78%
Left	13%
Both	9%
Physical activity	
Yes	35%
No	65%

Table 2. Clinical variables

Pain characteristics	Mean (standard deviation) or %
Sitting (yes)	82%
Squatting (yes)	67%
Running (yes)	61%
Jumping (yes)	61%
Up or downstairs (yes)	65%
Time of pain (months)	38.24 (49.97)
Knee in pain (dominance)	
Right	33%
Left	36%
Both	31%
FIQ (score, 0–16)	11.24 (3.4)
NPRS (score, 0–10)	4.54 (1.99)

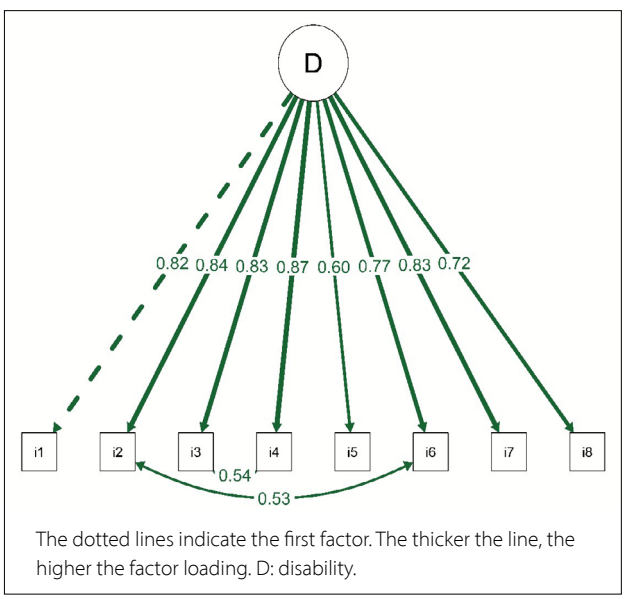
FIQ: Functional Index Questionnaire; NPRS: numerical pain rating scale.

Regarding the internal structure of the Brazilian version of the FIQ, the following fit indices were observed in the CFA: χ^2/DF = 2.08, TLI = 0.978, CFI = 0.969, RMSEA = 0.104 (90% confidence interval = 0.059–0.149), and SRMR = 0.077. Therefore, the one-dimensional structure with eight items presented RMSEA values above the 0.08 cutoff point, indicating a greater number of residuals than is acceptable for a model.

Using the fit indices within the CFA, we observed a high correlation between the following items: items 2 (climbing up two flights of stairs [16 steps]), 6 (climbing up four flights of stairs [32 steps]), 3 (squatting), and 4 (kneeling). This indicates a similarity in the response patterns for these items. We added these correlations to the model (**Figure 1**) and found the following suitable fit indices: χ^2/DF = 1.51, TLI = 0.990, CFI = 0.985, RMSEA = 0.072 (90% confidence interval = 0.000–0.124), and SRMR = 0.061.

DISCUSSION

We aimed to assess the structure of the FIQ using CFA in Brazilians with anterior knee pain and hypothesized that the unidimensional 8-item model of the FIQ is adequate. Our results, rejecting the hypothesis, showed that the one-dimensional structure with eight items presented more residuals than acceptable for the model. In addition, the high correlation between the items indicated a similarity in the response patterns for these items. Because of redundancy, this version of the FIQ should be used with caution and complemented by other similar assessment tools, such as the Kujala Score or the Anterior Knee Pain Scale.



The dotted lines indicate the first factor. The thicker the line, the higher the factor loading. D: disability.

Figure 1. Path diagram of the 8-item Functional Index Questionnaire (FIQ).

Reports on FIQ are limited. It was first reported at the Annual Congress of the Canadian Physiotherapy Association (Canada)[6] and has only been culturally adapted into two versions (Brazilian[3] and Persian[4]). Using the Persian version of the FIQ, Negahban et al.[4] performed factor analysis on a sample of 100 patients with patellofemoral pain syndrome. As a limitation of this study,[4] the authors recommended the assessment of responsiveness in subsequent studies. However, no researchers have investigated this measurement property in a Persian sample. Subsequently, in the Brazilian version of the FIQ, Cunha et al.[3] investigated internal and external responsiveness, as recommended by Negahban et al.[4] However, unlike the Persian version,[4] the Brazilian version of the FIQ[3] did not examine the internal structure through factor analysis.

This is the first study to assess the structure of the FIQ using CFA in Brazilian patients with anterior knee pain. However, some limitations of this study must be recognized to accurately interpret the results. First, the study population had a mean body mass index of 25.79 kg/m², and whether these results would vary in lean or obese Brazilians needs to be ascertained. Second, the study population had chronic pain with a mean time of 38.24 months and a mean pain level of 4.54 (NPRS) at the time of evaluation; hence, future studies should try to replicate our results in patients with acute pain needs. Third, the limited number of studies on this topic makes it difficult to compare our results.

Future studies should consider the redundancy of the items identified here and modify the instrument by proposing other functional activities that may cover different aspects of the lower limb function commonly performed by individuals with anterior knee pain, thus increasing the evaluative capacity of the FIQ.

CONCLUSION

This version of the FIQ should be used with caution because the unidimensional model of the questionnaire presents large residuals, mainly because of the redundancy among the items.

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Toward an algorithm of percutaneous microelectrolysis: a randomized clinical trial on invasive techniques

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Electric stimulation therapy.
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Myofascial pain syndromes.
Pain management.

ABSTRACT

BACKGROUND: Percutaneous microelectrolysis (MEP) is a minimally invasive technique used for pain relief, inflammation control, and tissue repair. However, the optimal treatment protocol remains under debate.

OBJECTIVE: To compare the effects of dry needling and MEP, with and without a treatment algorithm, on pain in individuals with active myofascial trigger points (MTrPs) in the upper trapezius muscle. Design and setting: Randomized controlled trial conducted at Maimónides University, Buenos Aires.

METHODS: Eighty-eight participants with MTrPs in the upper trapezius muscle were enrolled. The presence of MTrPs was confirmed through physical examination and algometric measurement before intervention. Participants were randomly assigned to one of six groups: Sham, dynamic dry needling, static dry needling, dynamic MEP, static MEP, or algorithmic MEP. Active treatments were administered using 0.30 mm × 40 mm acupuncture needles. Pain was assessed using two tools: the Numerical Pain Rating Scale (NPRS) and the Pressure Pain Threshold (PPT). Both measures were recorded with participants at rest before the intervention and again at 10 min, 24 h, 48 h, and 7 days post-intervention.

RESULTS: Significant post-intervention differences in NPRS scores were observed in all groups except dynamic dry needling when compared to Sham. The algorithmic MEP group achieved complete pain relief by day 7. In terms of PPT, the threshold values in the MEP groups were lower than those in the other groups.

CONCLUSIONS: All needling techniques demonstrated analgesic effects on myofascial trigger points, with the algorithm-enhanced MEP showing the most notable improvement in self-reported pain. However, MEP was not superior to other methods in improving pressure pain thresholds.

CLINICAL TRIALS: NCT05478928.

INTRODUCTION

Myofascial pain syndrome is a non-inflammatory disorder characterized by localized pain and stiffness, with the hallmark feature being the presence of myofascial trigger points (MTrPs).[1] While several diagnostic criteria exist, the primary indicator is muscle irritability triggered by pressure or stretching, which produces localized tenderness or referred pain. A palpable taut band may be detected, representing a localized muscle spasm.[1,2] The associated pain is typically constant and deep, and myofascial pain is considered a highly prevalent condition, often serving as a common reason for individuals to seek medical care.[3]

Several treatment modalities are available for this syndrome, including electrophysical agents.[4–6] One of the oldest such modalities is direct current (DC), also known as galvanic current, which is defined by its unidirectional flow. The energy accumulated in stimulated biological tissues during DC application promotes electrochemical changes, referred to as polar effects.[7] More recently, the use of DC in invasive applications has gained prominence in rehabilitation,[8,9] particularly through techniques such as percutaneous microelectrolysis (MEP).[10] MEP is a minimally invasive procedure in which low-intensity DC (up to 0.98 mA) is delivered via acupuncture needles, generating a high current density (approximately 3.8 mA/cm^2).[11] In addition to providing local analgesia, MEP is thought to induce a controlled inflammatory response that facilitates tissue repair. These physiological effects support its application in treating MTrPs, which are commonly found in the trapezius muscle among individuals with neck pain.[12]

However, the optimal intervention protocol for this therapy remains under debate, particularly regarding patient comfort during treatment. To address this, an algorithm has been proposed to minimize discomfort. Therefore, the aim of this study was to compare the effects of dry needling and percutaneous microelectrolysis, with or without the proposed algorithm, on pain in individuals with MTrPs in the upper trapezius muscle.

METHODS

Study design

This single-blind, randomized controlled trial was conducted using a convenience sample that included participants of both sexes, aged 18–48 years, with active MTrP, either unilateral or bilateral. Researcher 1, who was responsible for the statistical analysis, and the participants were blinded to group assignments. Recruitment, randomization, and group allocation were carried out by Researcher 2, who was not involved in participant assessment or intervention. Blocked randomization and blinded allocation were performed using the website: www.randomizer.org. Allocation concealment was ensured through sealed opaque envelopes, which were opened only by Researcher 3, responsible for administering the intervention, after the evaluation and immediately before the intervention. Both the participants and Researcher 3 remained unaware of the specific intervention until the treatment protocol was initiated. As a result, only the researcher performing the statistical analysis remained fully blinded throughout the study.

Ethical aspects

The study was approved by the Ethics Committee of Maimónides University (A-01-CEBBAD-20), in accordance with the Declaration of Helsinki and national ethical standards. The trial was registered on ClinicalTrials.gov (NCT05478928). All participants were fully informed about the nature, objectives, and procedures of the study, and each provided written informed consent. The study followed all guidelines outlined by the CONSORT 2010 (Consolidated Standards of Reporting Trials) statement.[13]

Participants

The criteria established by Simons et al.[1] and Gerwin et al.[14] were used to define MTrP: the presence of a taut band in the skeletal muscle, a hypersensitive spot within the taut band, a local contraction response upon palpation, and reproduction of referred pain when applying up to 3 kg/cm² of pressure on the trigger point.[15] These diagnostic criteria have demonstrated acceptable reliability, with κ values ranging from 0.36 to 0.882.[14] Participants were excluded if they had a history of neck or shoulder surgery, needle phobia, temporomandibular dysfunction, use of anticoagulants, concurrent treatment for MTrPs, fibromyalgia, endocrine disorders, pregnancy, or obesity (defined as a body mass index [BMI] greater than 28 kg/m²).[16]

Assessment procedures

Assessments were conducted before the first treatment session and at 10 min, 24 h, 48 h, and 7 days following the intervention. The following outcomes were evaluated: the Numerical Pain Rating Scale (NPRS) and the Pressure Pain Threshold (PPT). The primary outcomes of the study were pain intensity and pressure pain threshold at the MTrP.

Anamnesis and physical examination

During the anamnesis, the examiner collected demographic and clinical information, including personal data, weight (kg), height (m), BMI (kg/m²), occupation, history of illness, medication use, and any history of surgery or physical therapy.

Pain intensity was measured using the NPRS, a simple and validated tool consisting of a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain imaginable."[17]

The PPT was measured using an FDX® 25 algometer (Wagner Instruments, Greenwich, United States). A trained examiner placed the 1 cm² tip of the algometer perpendicular to the upper trapezius muscle fibers, bilaterally, just above the MTrP. Pressure was applied gradually at a rate of approximately 0.5 kg/cm²/s. This instrument has excellent intra- and inter-rater reliability (0.752 and 0.874, respectively).[18] Each site was compressed three times until the participant reported the onset of pain, and the average of the three readings (in kg/cm²) was recorded. Both PPT and NPRS assessments were performed while the participant was at rest, before the intervention, and again at 10 min, 24 h, 48 h, and 7 days post-intervention.

Intervention

Participants were randomly assigned to one of six groups: Sham, dynamic dry needling, static dry needling, dynamic MEP, static MEP, or algorithmic MEP.

In the dry needling groups, a single needle was inserted into the MTrP and positioned perpendicular to the upper trapezius trigger point for 120 s. In the static dry needling group, the needle remained stationary throughout the duration. In the dynamic dry needling group, needle movements were performed at a frequency of 1 Hz for the full 120 s.

In the MEP groups, a Sveltia DC device was used, connected to a dispersive electrode (area: 28.26 cm²) and an acupuncture needle (0.3 × 2.5 cm). The circuit was completed by placing the dispersive electrode on the arm contralateral to the trapezius muscle being treated. The current intensity at the needle was 0.6 mA, resulting in a current density of 2.53 mA/cm².

In the static MEP group, the needle was kept stationary for 120 s during active stimulation, delivering a total dose of 72 mC. In the dynamic MEP group, needle movements at 1 Hz were performed throughout the same period. If participants reported discomfort during any MEP intervention, the procedure was paused and resumed only once the discomfort subsided.

In the algorithmic MEP group, the needle was held stationary, but the treatment continued until the participant reported no

discomfort for more than 60 s. No predefined time limit exists for signal cessation. In the Sham group, a 0.3 × 25 mm acupuncture needle was inserted perpendicularly to a depth of 3 mm into the upper trapezius trigger point and held without movement for 120 s.

A detailed description of the algorithm is provided in **Figure 1**, and the intervention parameters for all interventions are summarized in **Table 1**.

The flowchart of the study development is shown in **Figure 2**.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (version 20.0, IBM Corp., Armonk, New York). Descriptive statistics were used to report the means and standard deviations of participant characteristics. The normality of the data was assessed using the Shapiro–Wilk test. A two-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the interaction between group and time. Results were

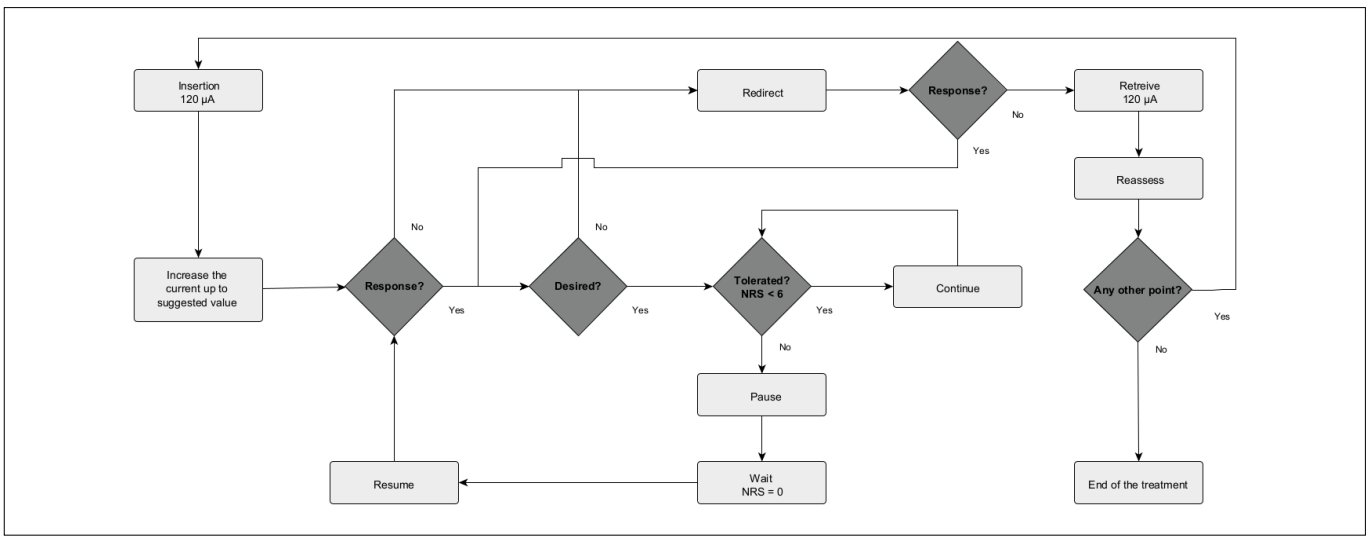

Figure 1. Proposed algorithm for the execution of percutaneous microelectrolysis.

Table 1. Parameters proposed for intervention

Parameters	DN Dynamic	MEP Dynamic	DN Static	MEP Static	MEP Static Alg.	Sham
Needle	0.3 × 2.5 cm	0.3 × 2.5 cm	0.3 × 2.5 cm	0.3 × 2.5 cm	0.3 × 2.5 cm	0.3 × 2.5 cm
Dispersive Electrode Area	–	28.26 cm^2	–	28.26 cm^2	28.26 cm^2	–
Frequency of movements	1 Hz	1 Hz	–	–	–	–
Current Intensity	–	0.6 mA	–	0.6 mA	0.6 mA	–
Time	120 s	120 s	120 s	120 s	variable	120 s
Total Dose	–	72 mC	–	72 mC	variable	–
Intervention Place	Perpendicular to the trigger point of the upper trapezius muscle					–

DN: Dry needling; MEP: Microelectrólisis Percutaneous; Alg.: Algorithm

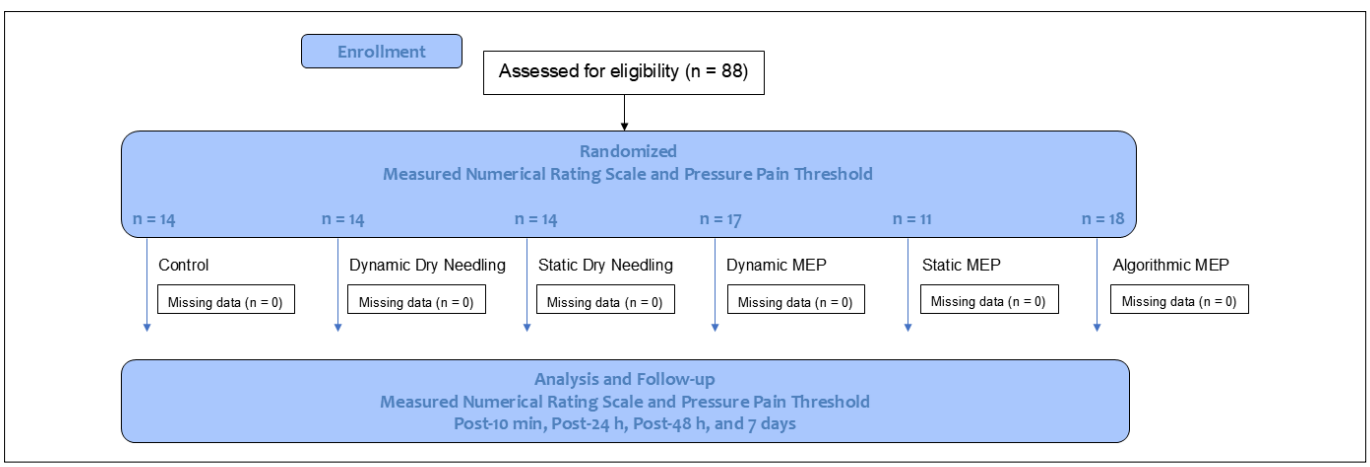

Figure 2. Research process flowchart.

reported as mean differences with 95% confidence intervals (95% CI) for the outcomes NPRS and PPT. Tukey's post hoc test was used for multiple comparisons, with the significance level set at P = 0.05. Data were reported as mean differences with corresponding standard errors. Effect sizes were calculated using Cohen's d, and interpreted according to Cohen's classification:[19] small (< 0.2), moderate (near 0.5), and large (> 0.8).

RESULTS

Compliance with the study protocol

The study initially planned to use the Visual Analog Scale; however, during implementation, the NPRS was adopted to improve participant understanding and streamline data collection. All participants completed their assigned intervention session. No participants reported receiving additional treatments during the study, and no adverse events were noted following any of the interventions.

Flow of participants through the study

A total of 88 participants (55 females) were recruited. The flow of participants and any loss to follow-up are illustrated in **Figure 2**.

Characteristics of the participants

Descriptive statistics for each intervention group are provided in **Table 2**. The six groups were well balanced at baseline. Most participants (62.5%) were female, and most were young adults.

Effects of the interventions

In group comparisons for the NPRS, significant post-intervention differences were observed across all groups, except for the dynamic dry needling group when compared to Sham. The Algorithmic MEP group was the only group to reach an NPRS score of 0 out of 10 on day 7, indicating complete resolution of pain. Regarding PPT, the MEP groups (Static, Dynamic, and Algorithmic) demonstrated lower thresholds compared to the other groups. All relevant data, along with the results of the two-way repeated measures ANOVA and corresponding effect sizes, are provided in **Tables 3 and 4**. Overall, the groups treated with percutaneous microelectrolysis showed superior outcomes on the NPRS. However, the dry needling groups exhibited better results for PPT. The Sham group consistently showed the least favorable clinical responses.

DISCUSSION

Several studies have examined the effects of MEP in the context of rehabilitation.[20–22] In the current study, in addition to evaluating clinical outcomes, we investigated the impact of incorporating an algorithm to guide a more targeted and patient-responsive treatment approach. The results demonstrated significant differences in both the NPRS and the PPT.

As discussed by D'Almeida et al.,[11] the MEP is considered a safe and effective therapeutic modality, a view supported by Ortiz et al.[7] and Ronzio et al.[10] Moreover, other studies have explored the analgesic effects and PPT outcomes of various MEP applications. For example, Al-Boloushi et al.[23] studied patients with plantar heel pain and found positive results in pain reduction, consistent with our findings. Similarly, favorable outcomes have been reported in conditions involving MTrPs, such as patellofemoral pain syndrome[21] and temporomandibular myofascial pain,[20] further supporting the clinical utility of percutaneous electrolysis. The observed benefits may be attributed to the mechanical effects of needle insertion and the chemical effects induced by the galvanic current, as previously described.

Table 2. Mean (SD; CI 95%) of demographic and clinical characteristics of participants

Outcomes	DN Dynamic	MEP Dynamic	DN Static	MEP Static	MEP Static Alg.	Sham
n	14	17	14	11	18	14
Sex (Female %)	9 (64.3)	13 (76.5)	8 (57.1)	9 (81.8)	7 (38.9)	9 (64.3)
Age (years)	37.1 (8.45;32.8–42.5)	20.9 (2.37;19.3–21.8)	34.9 (9.77;26.4–39.8)	18.7 (0.79;18.2–19.3)	20.2 (1.79;19–21.6)	28.9 (8.32;23.4–35.2)
Weight (kg)	79.1 (13.1;70.5–88.8)	69 (12.6;58.7–73)	79.3 (20.9;68.2–86.3)	61.5 (8.85;55.6–67.5)	64.4 (9.02;55.7–69.1)	75.4 (17.5;65.3–90.3)
Height (m)	1.69 (0.09;1.6–1.8)	1.67 (0.1;1.6–1.7)	1.7 (0.1;1.7–1.8)	1.65 (0.08;1.6–1.7)	1.71 (0.06;1.6–1.7)	1.73 (0.1;1.7–1.8)
BMI (kg/m^2)	27.7 (4.14;24.8–30.9)	24.8 (3.5;21.7–26.3)	27 (5.04;24–28.5)	22.5 (1.75;21.3–23.7)	22 (2.17;20.1–23.5)	25 (4.13;22.1–28.2)
PPT Pre	2.3 (0.58;1.8–2.7)	1.81 (0.58;1.3–2.1)	2.40 (0.37;2.1–2.6)	1.95 (0.65;1.4–2.4)	1.74 (0.54;1.2–1.9)	2.40 (0.25;2.4–2.3)
PPT Post-10 min	2.66 (0.36;2.5–2.8)	1.39 (0.54;1–1.8)	2.45 (0.3;2.3–2.7)	1.28 (0.67;0.7–1.7)	1.54 (0.61;1.1–1.8)	2.54 (0.35;2.2–2.8)
PPT Post-24 h	3.82 (1.98;2.4–5.6)	1.29 (0.47;0.9–1.5)	3.08 (0.75;2.4–3.6)	1.39 (0.52;1–1.8)	1.65 (0.45;1.4–2)	3.35 (1.5;2.2–4.8)
PPT Post-48 h	3.96 (2;2.4–5.7)	1.86 (0.60;1.4–2.1)	3.53 (0.98;2.6–3.9)	1.6 (0.69;1.1–2.1)	1.78 (0.56;1.4–2.2)	3.67 (1.42;2.7–5)
PPT Post-7 days	4.09 (2.21;2.4–6)	2.08 (0.93;1.4–2.5)	3.81 (0.93;2.9–4.2)	1.77 (0.75;1.2–2.3)	1.96 (0.65;1.6–2.2)	3.74 (1.51;2.7–5.2)
NPRS Pre	6.5 (1.79;5.5–8.1)	6.12 (2.12;3.6–6.8)	6.29 (2.09;4.7–7.5)	5.55 (1.37;4.5–6.5)	5.06 (1.34;3.7–5.9)	5.93 (2.59;4–7.8)
NPRS Post-10 min	6.93 (1.73;5.1–7.5)	3.18 (2.35;0.8–4.8)	5.5 (1.4;4.6–6.2)	2 (2.65;–0.1–3.9)	2.38 (1.93;0.6–3.2)	5.71 (2.3;3.7–7.3)
NPRS Post-24 h	4.29 (3.24;1.4–6.4)	3.29 (2.39;1.3–5.3)	4.29 (2.67;2.5–6.1)	1.09 (1.3;0.3–2.1)	0.94 (1.34;–0.2–1.8)	4.14 (3.63;1.3–6.9)
NPRS Post-48 h	3.57 (3.41;0.8–6.4)	0.88 (1.05;0.2–1.6)	3.71 (2.67;2.1–5.9)	0.27 (0.46;0–0.6)	0.31 (0.87;–0.4–1)	2.71 (3;0.6–4.6)
NPRS Post-7 days	2.5 (3.3;–0.1–5.1)	0.31 (0.79;–0.1–0.5)	2.64 (2.53;1.3–5.1)	0.45 (1.04;–0.3–1.3)	0 (0;0)	2.64 (3.13;0.3–4.5)

DN: Dry needling; MEP: Microelectrólisis Percutaneous; Alg.: Algorithm; BMI: Body Mass Index; PPT: Pressure Pain Threshold; NPRS: Numeric Pain Rating Scale; Values are reported as mean (SD)

Table 3. Outcomes of the interactions between time and group variables for Numerical Pain Rating Scale (NPRS) and Pressure Pain Threshold (PPT)

Pressure Pain Threshold							
Moment	**Comparison**	**Mean Diff.**	**Std. Error**	**P value**	**95% CI for difference**		**d_{cohen}**
					Lower	**Upper**	
Pre	Sham vs. MEP Static Alg.	0.838	0.173	0.014	0.155	1.521	–
	DN Static vs. MEP Static Alg.	0.800	0.163	0.013	0.154	1.446	–
Post-10 min	Sham vs. MEP Dynamic	1.125	0.254	0.025	0.122	2.128	−1.18
	Sham vs. MEP Static	1.288	0.256	0.011	0.275	2.301	−0.277
	Sham vs. MEP Static Alg.	1.041	0.247	0.034	0.065	2.017	−0.756
	DN Dynamic vs. MEP Dynamic	1.265	0.243	0.008	0.303	2.227	1,31
	DN Dynamic vs. MEP Static	1.428	0.213	0.001	0.587	2.269	1.629
	DN Dynamic vs. MEP Static Alg.	1.181	0.188	0.002	0.438	1.924	0.979
	MEP Dynamic vs. DN Static	−1.078	0.234	0.019	−2.003	−0.153	−0.921
	DN Static vs. MEP Static	1.241	0.222	0.005	0.361	2.121	1.363
	DN Static vs. MEP Static Alg.	0.994	0.207	0.014	0.177	1.811	0.514
Post-24 h	DN Hong vs. MEP Dynamic	2.787	0.600	0.018	0.413	5.161	−3.425
	MEP Dynamic vs. DN Static	−1.801	0.241	0.001	−2.752	−0.850	2.352
	DN Static vs. MEP Static	1.609	0.194	0	0.830	2.388	−2.347
	DN Static vs. MEP Static Alg.	1.274	0.321	0.049	0.005	2.543	−1.584
Post-48 h	Sham vs. MEP Static	2.227	0.499	0.024	0.253	4.201	−3.347
	Sham vs. MEP Static Alg.	2.038	0.512	0.048	0.013	4.063	−2.734
	MEP Dynamic vs. DN Static	−1.486	0.326	0.021	−2.776	−0.196	−2.117
	DN Static vs MEP Static	1.613	0.343	0.017	0.257	2.969	−3.102
	DN Static vs. MEP Static Alg.	1.424	0.324	0.026	0.141	2.707	−2.242
Post 7 days	DN Static vs. MEP Static	1.786	0.253	0.001	0.785	2.787	−3.009
	DN Static vs. MEP Static Alg.	1.599	0.344	0.018	0.240	2.958	−2.448

Table 4. Numeric pain rating scale

Moment	**Comparison**	**Mean Diff.**	**Std. Error**	**P value**	**95% CI for difference**		**d_{cohen}**
					Lower	**Upper**	
Post-10 min	Sham vs. MEP Static Alg.	3.600	0.763	0.016	0.583	6.617	−1.21
	DN Dynamic vs. MEP Static Alg.	4.400	0.792	0.005	1.270	7.530	−1.954
	DN Static vs. MEP Static	3.500	0.792	0.025	0.367	6.633	−1.473
	DN Static vs. MEP Static Alg.	3.500	0.719	0.013	0.658	6.342	−1.08
Post-24 h	DN Static vs. MEP Static	3.100	0.706	0.026	0.307	5.893	−1.313
	DN Static vs. MEP Static Alg.	3.500	0.860	0.042	0.101	6.899	−1.211
Post-48 h	MEP Dynamic vs. DN Static	3.100	0.767	0.044	0.068	6.132	1.23
	DN Static vs. MEP Static	3.700	0.817	0.021	0.469	6.931	−1.441
	DN Static vs. MEP Static Alg.	3.700	0.857	0.029	0.311	7.089	−1.24

However, unlike other studies,[7] our investigation did not find significant improvements in PPT among the MEP groups. We hypothesize that the inflammatory response triggered by DC may have sensitized the treated area, leading to reduced pressure tolerance and, consequently, lower PPT values.[10]

An important point of discussion is that various forms of therapeutic electrolysis are currently under investigation, all of which are based on their ability to induce a localized and controlled inflammatory response within the treatment area. This response is consistently highlighted as a superior mechanism for modulating collagen synthesis and enhancing local circulation, thereby promoting tissue repair and pain relief. However, a key distinguishing factor among these techniques is the intensity of the electrical current used. The model employed in this study utilized microampere (μA) intensity, which is known to provide greater comfort during the intervention. Furthermore, the current findings align with the observations of Ortiz et al.,[24] who emphasize the need for clearer standardization of treatment doses and protocols. In this context, the algorithm used in our study supports a more targeted and effective clinical approach based on current evidence.

All intervention groups showed analgesic effects, but only the algorithm group reached a pain score of zero by day 7. Including this group in future studies is strongly recommended, along with a larger sample size to validate these findings. The analgesic effects observed align with those reported in a recent systematic review.[25] Therefore, the use of such an algorithm appears to be a valuable

complement to invasive electrotherapy techniques. Nevertheless, this study has limitations, including a relatively small sample size and a lack of control for hormonal phase variations among female participants,[26,27] which should be considered when interpreting the results.

Clinical relevance

- Needling techniques demonstrate analgesic effects on myofascial trigger points.
- The use of the proposed algorithm in conjunction with percutaneous microelectrolysis enhanced the analgesic effects.
- With regard to pressure pain threshold, the outcomes for the three percutaneous microelectrolysis techniques (Static, Dynamic, and Algorithmic) were comparable.

CONCLUSION

Needling techniques produce analgesic effects on myofascial trigger points, particularly when combined with the proposed algorithm. However, in terms of pressure pain threshold, the addition of microelectrolysis did not demonstrate superior results.

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Psychological distress among university students during remote learning in Brazil: a multicenter online study

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ABSTRACT

BACKGROUND: Studies assessing the prevalence of mental disorders in the context of remote teaching in Brazil during the coronavirus disease (COVID-19) pandemic are scarce.

OBJECTIVE: To estimate the prevalence of symptoms of anxiety and depression and their relationship with sociodemographic characteristics among university students during the COVID-19 pandemic.

DESIGN AND SETTING: This multicenter cross-sectional study was conducted at eight Brazilian public universities.

METHODS: This study was conducted on students regularly enrolled in undergraduate courses. Data were collected between October 2021 and February 2022 using an online self-administered questionnaire that addressed sociodemographic and academic characteristics, lifestyle habits, and health conditions. Anxiety and depression symptoms were assessed using the Depression, Anxiety, and Stress Scale-21. The variables were analyzed descriptively using frequency distribution, proportion, 95% confidence interval (95% CI), and Pearson's chi-squared test.

RESULTS: A total of 8,650 students participated, and most of them were women, white, heterosexual, cisgender, and unmarried, with a mean age of 23.9 (standard deviation: ± 6.34) years and living with family members. Symptoms of anxiety and depression were observed in 59.7% (95% CI: 58.7–60.7) and 63.0% (95% CI: 62.0–64.0) of the students, respectively. These symptoms were associated with sex, age, skin color, sexual orientation, gender identity, marital status, education of the head of the family, family income, decrease in income during the pandemic, and area of knowledge.

CONCLUSION: Most university students showed symptoms of anxiety and depression during the suspension of face-to-face activities in universities, indicating the need for institutional actions and public policies aimed at promoting their health and mental well-being.

INTRODUCTION

Anxiety and depression are among the most prevalent mental health disorders, particularly in low-income countries. In 2015, an estimated 300 million people were reported with depression, equivalent to 4.4% of the world's population. The estimated number of people with anxiety disorders worldwide is 264 million, totaling 3.6% of the population.[1] The coronavirus disease (COVID-19) pandemic caused widespread concerns and raised several questions on its impacts on mental health, driven by direct psychological effects and short- and long-term social and economic consequences in the population.[2,3]

In response to the COVID-19 pandemic, universities suspended face-to-face activities for a period and later adopted remote teaching. Studies indicate that this strategy resulted in psychological consequences among university students, possibly due to the interruption of academic routines, which compromised the progress of undergraduate courses, caused uncertainty regarding future careers, and impacted social life as interpersonal interactions were affected.[4,5]

Moreover, prior to the pandemic, university students were identified as a group susceptible to episodes of anxiety and depression at any stage of their academic life, owing to their vulnerability to psychosocial stressors related to the challenges of their academic routine and to various changes occurring in their lives.[6,7] The intensification of study hours and increased self-demand are factors that may worsen students' psychological state.[8] However, most studies that assess the

prevalence of symptoms of anxiety and depression among university students are restricted to particular academic courses, such as in the health area, limiting the extrapolation of results to the university student population in general.[9–11]

Thus, considering that university students are vulnerable to the effects of the COVID-19 pandemic, particularly with regard to mental health, the prevalence of mental disorders in this population needs to be determined during emergency remote teaching. Such information can help us understand the factors related to an increase in the prevalence of mental disorders among university students. It shall support the development and improvement of strategies and actions for structuring supportive and inclusive environments aimed at improving the physical and mental well-being of university students, considering the resumption of face-to-face academic activities.

OBJECTIVE

This study aimed to estimate the prevalence of symptoms of anxiety and depression and their relationship with sociodemographic characteristics among university students from the Federal Institutions of Higher Education (IFES) in Brazil during the COVID-19 pandemic.

METHODS

Study design and population

The study "Symptoms of anxiety and depression disorder among university students in Minas Gerais: Prevalence and associated factors," also called the Project on Anxiety and Depression in University Students (PADu multicenter), is a multicenter survey conducted among undergraduate students from eight universities in the state of Minas Gerais.

All students who were regularly enrolled in the second half of 2021 at the eight IFES were invited to participate in the survey, and 118,828 undergraduate students were considered eligible. The PADu multicenter dataset comprised valid information from 8,650 students, with a response rate of 7.3%. **Figure 1** shows a flowchart of university student participation.

The inclusion criteria were age ≥ 18 years, students enrolled in any undergraduate course at the eight IFES participating in the project, and those enrolled in any academic period. Students who did not complete the questionnaire, postgraduate and residency students, or those who were regularly enrolled but did not participate in academic activities or were on exchange during data collection were excluded from the survey. As the questionnaire was online and any student could access it through social networks, graduate students and residents participated in this study. Only data from undergraduate students who met the inclusion criteria were retained.

Data collection

Data collection was conducted between October 2021 and February 2022, which lasted for three months at each participating IFES. The study was approved by the Research Ethics Committees of all participating universities.

The survey was widely publicized on the websites and social networks of the IFES and PADu (@padufederais), in addition to tutoring programs, laboratories, study and research groups, centers, and academic directories. As a communication and recruitment strategy for participants, a visual identity was developed and applied to all promotional materials, social networks, questionnaires, and materials used by the team.

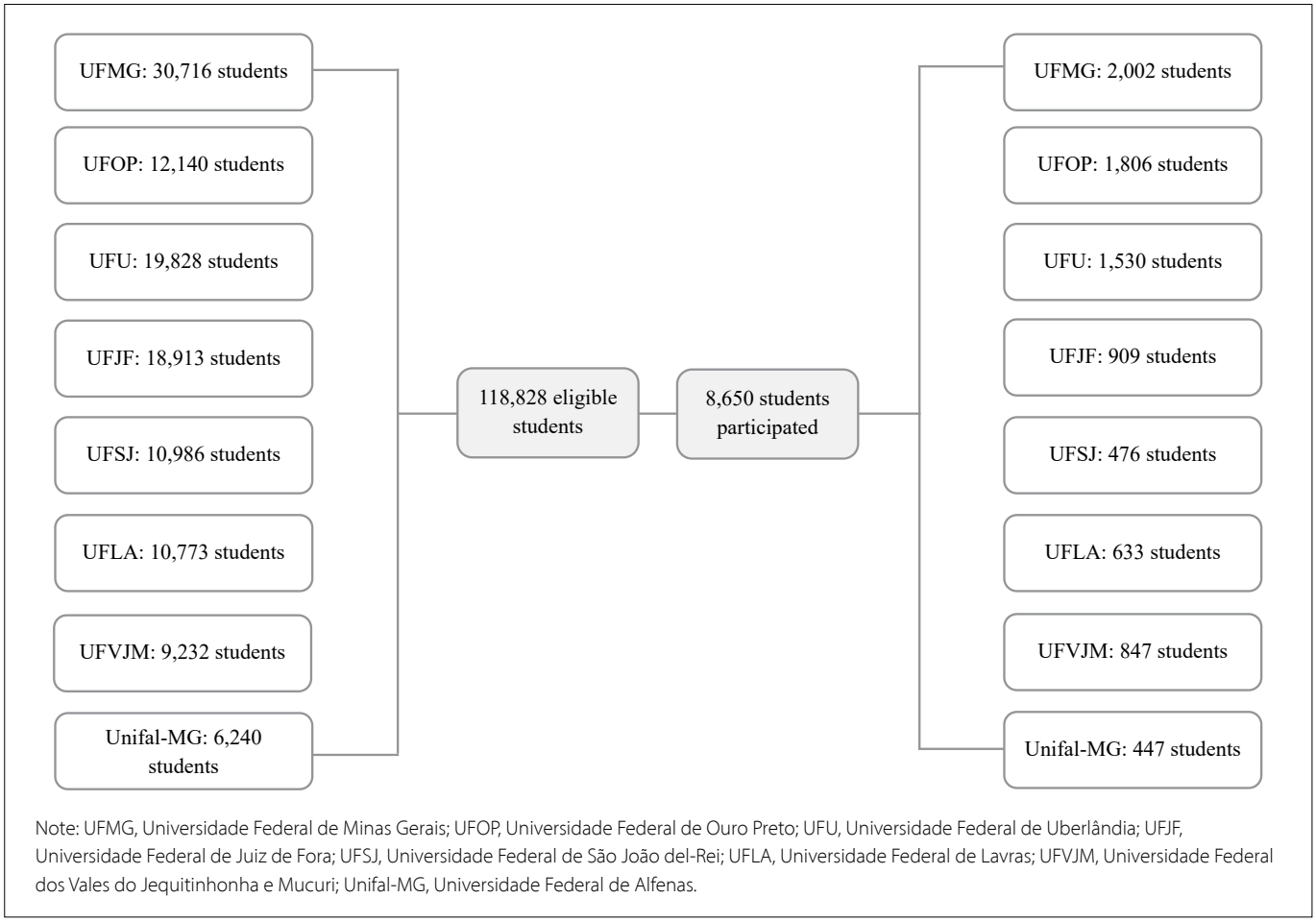
Students received an invitation text and a link to access the self-administered confidential questionnaire via email, which was available on Google Forms. Participation in the study was initiated when accessing the questionnaire upon agreement through an online check of the Free and Informed Consent Form presented electronically and available for download. All questionnaire items were presented, detailing important points and possible areas of confusion.

For data collection, the study required the participation of postgraduate students (doctoral and master's students) and scientific initiation. Each IFES has a reference researcher and at least one graduate or scientific initiation student to assist with the project. The team received prior training from the coordinating center (Universidade Federal de Ouro Preto [UFOP]) to standardize data collection at different IFES. During training, the researchers were informed of the importance of the research, topics addressed in the questionnaire, and the methodological criteria of the study, in addition to the method of sending the questionnaire link and approaching individuals for dissemination. In addition, a field manual containing information about the project, general instructions for collection, schedule of activities, and sending of e-mails, was prepared. The entire data collection process was monitored by a general research coordinator, aiming to maintain consistency in data collection procedures and homogeneity of information, and consequently to obtain reliable data and reduce the chance of possible errors and biases, such as duplicates and typographical errors.

Data collection instrument

The questionnaire used in the PADu multicenter study included questions specifically designed for the study, which were prepared by a team of researchers, and questions used in national surveys. Questions related to general, sociodemographic, and academic characteristics; lifestyle habits; health conditions; social support; quality of life; and resilience were included (**Table 1**).[12–31]

To select the investigated topics, the researchers considered the available evidence regarding the outcomes of interest, comparability with similar studies, validated instruments with open access, and meeting the research objectives of the eight IFES.



Note: UFMG, Universidade Federal de Minas Gerais; UFOP, Universidade Federal de Ouro Preto; UFU, Universidade Federal de Uberlândia; UFJF, Universidade Federal de Juiz de Fora; UFSJ, Universidade Federal de São João del-Rei; UFLA, Universidade Federal de Lavras; UFVJM, Universidade Federal dos Vales do Jequitinhonha e Mucuri; Unifal-MG, Universidade Federal de Alfenas.

Figure 1. Flowchart of student participation by university. Minas Gerais, 2021–2022.

Study variables

The presence of symptoms of anxiety and depression in the health condition block was assessed using the Portuguese version of the Depression Anxiety Stress Scale-21 (DASS-21), adapted and validated by Vignola and Tucci. The DASS-21 is a self-reported test composed of a set of three independent subscales, with seven questions each. The scale assesses symptoms of anxiety, depression, and stress presented by individuals in the last week, that is, the week prior to data collection, through the total scores obtained in the subscales.[27] The subscale items are divided as follows: the depression subscale includes questions 3, 5, 10, 13, 16, 17, and 21; the anxiety subscale includes questions 2, 4, 7, 9, 15, 19, and 20; and the stress subscale includes questions 1, 6, 8, 11, 12, 14, and 18.[32]

Responses to the items were structured on a four-point Likert-type scale ranging from 0 (did not apply at all) to 3 (applied a lot or most of the time). The answers "applied to some degree or for a short time" and "applied to a considerable degree or for a good part of the time" refer to scores 1 and 2, respectively. The scores for anxiety and depression are generated from the total scores and are then multiplied by 2, generating the classification levels as "normal," "mild," "moderate," "severe," and "extremely severe."

In the present study, only symptoms of anxiety and depression were evaluated. Based on the classification presented above, the "moderate," "severe," and "extremely severe" levels were recategorized as "moderate-to-extremely severe" and the "normal" and "mild" levels as "normal and mild."

The sociodemographic variables used to describe the sample included sex (male and female), age (18–20, 21–22, 23–25, and ≥ 26 years of age), skin color (white, brown, black, and yellow, indigenous, and others), sexual orientation (heterosexual, homosexual, bisexual, asexual, and others), gender identity (cisgender, transgender, and non-binary), marital status (single, married/stable union, widowed, and divorced), housing (with and without family members), education of the head of the family (no education or incomplete primary education, complete primary education or incomplete secondary education, complete secondary education or incomplete higher education, and complete higher education), total family income (≤ 1 to 2 minimum wages, 3 to 5 minimum wages, 6 to 10 minimum wages, and > 10 minimum wages), and

Table 1. Topics included in the questionnaire of the Project on Anxiety and Depression among University Students, 2021–2022

Modules	Variables	References
Student identification	Enrollment,* course, and institution.	Questions prepared by the project researchers.
General characteristics and socioeconomic conditions	Age, city of residence and housing, race, biological sex, gender identity, sexual orientation, level of education of the head of the family, marital status, family income, and religious belief.	Questions taken from and/or based on the Instituto Brasileiro de Geografia e Estatística[12] and Pesquisa Nacional de Saúde (PNS)[13] census.
Life habits	Number of participants in remote teaching, difficulties in dealing with the pandemic, and study routine. Consumption of alcohol, tobacco, and illicit substances. Practice of physical exercise and sedentary behavior. Frequency and eating habits, self-efficacy for adopting healthy practices, emotional eating, body image issues, and dysfunctional eating attitudes.	Questions prepared by the project researchers. Questions taken from and/or based on the Instituto Brasileiro de Geografia e Estatística,[12] PNS,[13] and Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (VIGITEL)[14] census. Questions based on VIGITEL.[14] Instrument constructed from items addressed in previous research with adolescents and young adults.[15–21] The Three Dietary Factors Questionnaire was used to analyze the profile of eating behavior according to the emotional eating subscale score.[22] The translated and validated version for the Brazilian population was used.[23] Simplified questionnaire of dysfunctional eating attitudes based on the study by Ferreira and Veiga (2008).[24]
Health conditions	General health aspects, such as self-reported weight and height, presence of morbidities, self-rated health, suicidal ideation, and medication use.	Questions taken and/or adapted from the PNS,[13] use of medication adapted from the study by Bertoldi et al.,[25] and study of self-injury adapted from Fonseca et al.[26]
Anxiety, depression, and stress scale	Variables that assess symptoms of anxiety, depression, and stress.	Depression Anxiety Stress Scale-21, translated and validated by Vignola and Tucci.[27]
Social support scale	Variables that assess social support.	Social support satisfaction scale, version adapted from Ribeiro[28] and Zanini et al.[29]
Quality of life scale	Variables that assess quality of life.	Quality of life determines World Health Organization Quality of Life abbreviated version, translated and validated by Fleck et al.[30]
Resilience scale	Variables that assess resilience.	Connor–Davidson Resilience Scale, translated and validated by Lopes and Martins.[31]

* The UFU Research Ethics Committee did not authorize the collection of this information to avoid identifying students.

decrease in family income in the three months prior to the survey (no and yes). The salary value considered in this study refers to the minimum wage in force in 2021 (R$ 1,100).

Academic aspects related to the area of knowledge in the course (life sciences, exact sciences, and human, social, and applied sciences) were also investigated and used to describe the data.

Statistical analyses

The use of an online questionnaire enabled the development of an automatic database that was exported to Microsoft Excel 2013. Subsequently, data coding and consistency analyses were performed to ensure the quality and validity of the information.

For sample characterization and data comparison, variables were analyzed using frequency distribution and Pearson's chi-squared test. The proportion and 95% confidence interval (95% CI) were used to estimate the prevalence of symptoms of anxiety and depression. Statistical significance was set at 5%. Analyses were performed using the Stata statistical software (version 13.0; Stata Corporation, College Station, TX, USA).

Ethical aspects

The PADu multicenter study was conducted according to the guidelines established by the Declaration of Helsinki and was approved by the Research Ethics Committee of the coordinating center (UFOP) under protocol number 43027421.3.1001.5150 and by the Ethics Committees of all institutions (Universidade Federal de Minas Gerais [UFMG]: 43027421.3.2004.5149; Universidade Federal de Uberlândia [UFU]: 43027421.3.2001.5152; Universidade Federal de Juiz de Fora [UFJF]: 43027421.3.2003.5147; Universidade Federal de São João del-Rei [UFSJ]: 43027421.3.2002.5545; Universidade Federal de Lavras [UFLA]: 43027421.3.2006.5148; Universidade Federal dos Vales do Jequitinhonha e Mucuri [UFVJM]: 43027421.3.2009.5108; and Universidade Federal de Alfenas [Unifal-MG]: 43027421.3.2008.5142). All participants were duly informed about voluntary collaboration and guaranteed anonymity, research objectives, steps to be undertaken, and risks and benefits of their participation before signing the Free and Informed Consent Term and approval by the Ethics Committees.

RESULTS

Of the 8,650 participating students, the majority were women, with a mean age of 23 years and 9 months (standard deviation ± 6.34 years), white, heterosexual, cisgender, single, and living with family members. Approximately 41.0% of the students reported a family income of three to five times the minimum wage, and 51.6% reported a decrease in family income three months prior to data collection. Regarding the education of the family head, 39.4% of the students reported completing higher education. Students reported being enrolled in courses in the following areas of knowledge: 39.5% exact sciences, 31.9% life sciences, and 28.9% human, social, and applied sciences. **Table 2** presents the main sociodemographic and academic characteristics of the participants.

Univariate analysis (**Table 2**) showed that sex, age, skin color, sexual orientation, gender identity, marital status, education of the family head, family income, decrease in family income, and area of knowledge were related to symptoms of anxiety and depression among the students ($P < 0.050$).

Among the participants, 59.7% (95% CI: 58.7–60.7) were classified as having anxiety symptoms; of them, 33.9% had extremely severe symptoms. The prevalence of symptoms of depression among students was 63.0% (95% CI: 62.0–64.0); of them, 32.5% were classified as having extremely severe symptoms (**Figure 2**).

Figure 3 shows the prevalence of symptoms of anxiety and depression according to their severity. Students from the UFOP had a higher proportion of absence of symptoms of anxiety (40.8%) and depression (32.1%), considering the normal classification, and a lower proportion of extremely severe symptoms of both anxiety (29.3%) and depression (26.5%). When compared to the IFES, a higher prevalence of extremely severe anxiety symptoms was observed among students from Unifal-MG (38.9%) and UFVJM (37.7%). However, a higher proportion of students with symptoms of extremely severe depression was observed in the UFMG (35.4%) and UFJF (35.7%).

DISCUSSION

The results of this study indicated a high prevalence of symptoms of mental disorders among students investigated at the eight IFES in Minas Gerais during the COVID-19 pandemic. In addition, a significant difference was observed in the prevalence of moderate-to-extremely severe symptoms of anxiety and depression in relation to sociodemographic and academic characteristics.

During the COVID-19 pandemic, high prevalence rates of mental disorders have been estimated in the world population. Different meta-analyses indicate prevalences between 26.9–38.1% and 28.0–34.3% for symptoms of anxiety and depression in the general population, respectively.[33–36] In the pandemic context, Santomauro et al.[3] indicated an increase of 25.6% in anxiety diagnoses and 27.6% in new cases of depression. In a household epidemiological survey conducted on adults over 18 years of age during the pandemic between October and December 2020 in two cities in the state of Minas Gerais, the presence of anxiety symptoms was observed in 23.3% of participants and depression symptoms in 15.6%.[37]

In the university population, the prevalence of anxiety and depression during the pandemic was similar to or higher than that in the general population,[38,39] corroborating the findings of the present study. The results indicate an increase in the prevalence of mental disorders among university students during the COVID-19 pandemic when compared to studies conducted before this period.[40,41] In a study conducted in 2019 on students in the first semester at a public university, which used the DASS-21 scale, De Paula et al.[40] observed that the self-reported prevalence of symptoms of anxiety and depression among university students was 42.5% (95% CI: 37.4–47.7) and 33.2% (95% CI: 28.3–38.2), respectively, suggesting lower levels of mental disorders than those found in the present study during the pandemic.

In a survey of students at a university in the United States in the first half of 2020, Wang et al.[42] found that 48.1% of undergraduate and graduate students had moderate-to-severe depression, whereas 38.5% of students had mild-to-severe anxiety. The authors also found that most participants (71.3%) reported increased stress and anxiety levels during the COVID-19 pandemic owing to the abrupt transition and maintenance of online classes, concerns about grades, and late graduation. The prevalences found by Wang et al.[42] are lower than those found in the present study; however, they showed an increased prevalence of mental disorders among university students during the pandemic.

Thus, the physical closure of educational institutions and the suspension of face-to-face activities during the COVID-19 pandemic resulted in challenges for the academic community and society,[43] with psychological implications for university students.[5] The period of distance teaching and learning was unprecedented and could have resulted in psychological consequences among university students.[4,43] The higher prevalence of symptoms of anxiety and depression in this population could be a consequence of the drastic change in the routine of the university community, with significant effects in the short and long terms.

In the present study, the estimates of the prevalence of symptoms of anxiety and depression varied according to the sociodemographic and academic characteristics of university students, such as sex, age, skin color, sexual orientation, gender identity, marital status, education of the family head, family income, decreased income during the pandemic, and area of knowledge. Evidence shows that mental disorders are more prevalent among female students, those who are older and of low socioeconomic status, those among ethnic, racial, and sexual minorities (homosexual

Table 2. Sociodemographic characteristics of university students according to the presence of symptoms of anxiety and depression during the COVID-19 pandemic. Project on Anxiety and Depression in University Students, 2021–2022 (n= 8,650)

Variables	Total (n, %)	Anxiety symptoms		P value*	Depression symptoms		P value*
		Normal and mild (n = 3,486)	Moderate to extremely severe (n = 5,164)		Normal and mild (n = 3,201)	Moderate to extremely severe (n = 5,449)	
Biological sex (n = 8,615)							
Male	2,955 (34.3)	1,560 (52.8)	1,395 (47.2)	**< 0.001**	1,234 (41.8)	1,721 (58.2)	**< 0.001**
Female	566 (65.7)	1,913 (33.8)	3,747 (66.2)		1,959 (34.6)	3,701 (66.4)	
Age							
18–20 years	2,552 (29.5)	969 (38)	1,583 (62)	**< 0.001**	977 (38.3)	1,575 (61.7)	**0.006**
21–22 years	2,135 (24.7)	855 (40)	1,280 (60)		789 (37)	1,346 (63)	
23–25 years	2,000 (23.1)	759 (38)	1,241 (62)		677 (33.9)	1,323 (66.1)	
≥ 26 years	1,963 (22.7)	903 (46)	1,060 (54)		758 (38.6)	1,205 (61.4)	
Skin color (n = 8,474)							
White	4,694 (55.4)	1,953 (41.6)	2,741 (58.4)	**0.016**	1,833 (39)	2,861 (61)	**< 0.001**
Brown	2,622 (30.9)	1,047 (39.9)	1,575 (60.1)		961 (36.7)	1,661 (63.3)	
Black	1,039 (12.3)	382 (36.8)	657 (63.2)		307 (29.6)	732 (70.4)	
Yellow, Indigenous, and others	119 (1.4)	55 (46.2)	64 (53.8)		45 (37.8)	74 (62.2)	
Sexual orientation (n = 8,374)							
Heterosexual	5,714 (68.2)	2,614 (45.8)	3,100 (54.2)	**< 0.001**	2,412 (42.2)	3,302 (57.8)	**< 0.001**
Homosexual	753 (9)	254 (33.7)	499 (66.3)		217 (28.8)	536 (71.2)	
Bisexual	1,685 (20.1)	467 (27.7)	1,218 (72.3)		448 (26.6)	1,237 (73.4)	
Asexual and others	222 (2.7)	51 (23)	171 (77)		37 (16.7)	185 (83.3)	
Gender identity (n = 8,433)							
Cisgender	8,211 (97.4)	3,353 (40.8)	4,858 (59.2)	**< 0.001**	3,075 (37.4)	5,136 (62.6)	**< 0.001**
Transgender	59 (0.7)	17 (28.8)	42 (71.2)		24 (40.7)	35 (59.3)	
Non-binary	163 (1.9)	42 (25.8)	121 (74.2)		30 (18.4)	133 (81.6)	
Marital status							
Single	7,775 (90.6)	3,067 (39.4)	4,708 (60.6)	**< 0.001**	2,819 (36.3)	4,956 (63.7)	**< 0.001**
Married/stable union	709 (8.3)	356 (50.2)	353 (49.8)		321 (45.3)	388 (54.7)	
Widowed and divorced	98 (1.1)	42 (42.9)	56 (57.1)		44 (44.9)	54 (55.1)	
Housing							
Without family members	2,048 (23.7)	2,697 (40.9)	3,905 (59.1)	0.061	2,467 (37.4)	4,135 (62.6)	0.211
With family members	6,602 (76.3)	789 (38.5)	1,259 (61.5)		734 (35.8)	1,314 (64.2)	
Education of the head of the family (n = 8,528)							
No education or incomplete primary education	1,297 (15.2)	429 (33.1)	868 (66.9)	**< 0.001**	405 (31.2)	892 (68.8)	**< 0.001**
Complete primary education or incomplete secondary education	941 (11)	371 (39.4)	570 (60.6)		342 (36.3)	599 (63.7)	
Complete secondary education or incomplete higher education	2,931 (34.4)	1,171 (40)	1,760 (60)		1,035 (35.3)	1,896 (64.7)	
Complete higher education	3,359 (39.4)	1,463 (43.6)	1,896 (56.4)		1,381 (41.1)	1,978 (58.9)	
Total family income**							
≤ 1–2 minimum wages	2,595 (32.1)	812 (31.3)	1,783 (68.7)	**< 0.001**	754 (29.1)	1,841 (70.9)	**< 0.001**
3–5 minimum wages	3310 (40.9)	1,383 (41.8)	1,927 (58.2)		1,219 (36.8)	2,091 (63.2)	
6–10 minimum wages	1,397 (17.3)	642 (46)	755 (54)		603 (43.2)	794 (56.8)	
> 10 minimum wages	788 (9.7)	416 (52.8)	372 (47.2)		404 (51.3)	384 (48.7)	
Drop in family income (n = 8,195)							
No	3,966 (48.4)	1,854 (46.8)	2,112 (53.2)	**< 0.001**	1,704 (43)	2,262 (57)	**< 0.001**
Yes	4,229 (51.6)	1,463 (34.6)	2,766 (65.4)		1,332 (31.5)	2,897 (68.5)	
Area of knowledge							
Exact Sciences	3,416 (39.5)	1,494 (43.7)	1,922 (56.3)	**< 0.001**	1,310 (38.3)	2,106 (61.7)	**< 0.001**
Life Sciences	2,731 (31.6)	1,151 (42.1)	1,580 (57.9)		1,092 (40)	1,639 (60)	
Humanities and Social and Applied Sciences	2,503 (28.9)	841 (33.6)	1,662 (66.4)		799 (31.9)	1,704 (68.1)	

Note: Variables with n less than 8,650 differ from the total study sample because of missing responses. * P value obtained by chi-squared test; values in bold indicate statistically significant variables. ** Minimum wage in force in Brazil in 2021 = R$ 1,100.

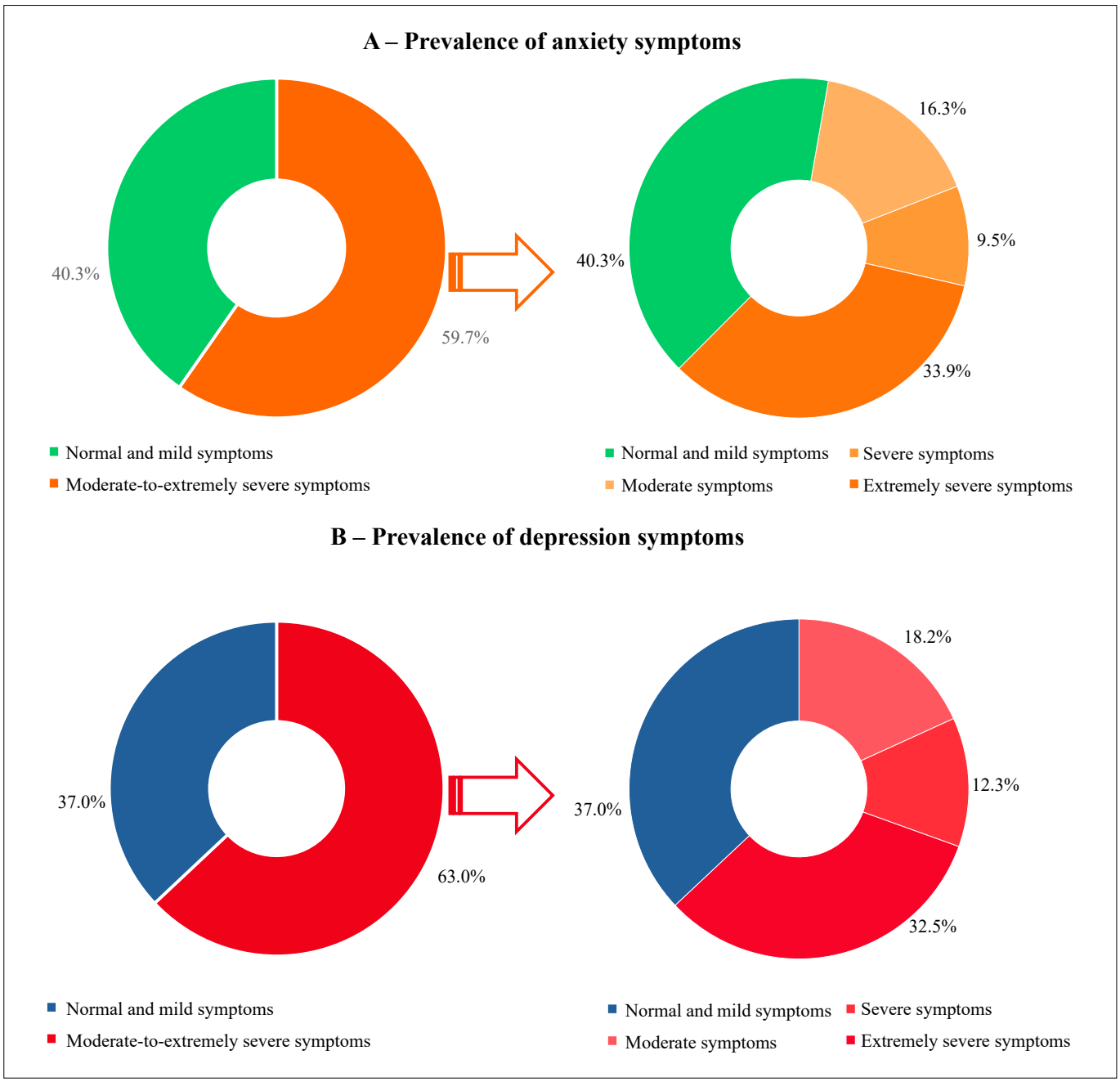


Figure 2. Prevalence of symptoms of anxiety and depression in university students. Project on Anxiety and Depression in University Students, 2021–2022 (n = 8,650).

and bisexual), and students in health courses.[40,41,44,45] For example, gender differences may be correlated with personal stigma, vulnerability, prejudice, and gender discrimination, in addition to the fact that non-heterosexual women recognize symptoms of depression better and seek more help from counseling and health services than men and heterosexual women.[41,45]

The findings of this study are consistent with those of other studies conducted in the context of the pandemic, demonstrating that culturally disadvantaged and vulnerable groups, such as women, those of black origin and minority ethnicity, those with lower socioeconomic status, and those among sexual minorities, have a higher prevalence of symptoms of anxiety and/or depression.[2,46] Studies conducted on students in France between April and May 2020 observed that being of a female or nonbinary gender, reporting a decrease in income, poor-quality housing, and not living with family members were risk factors associated with mental health problems among students who experienced the COVID-19 pandemic.[46]

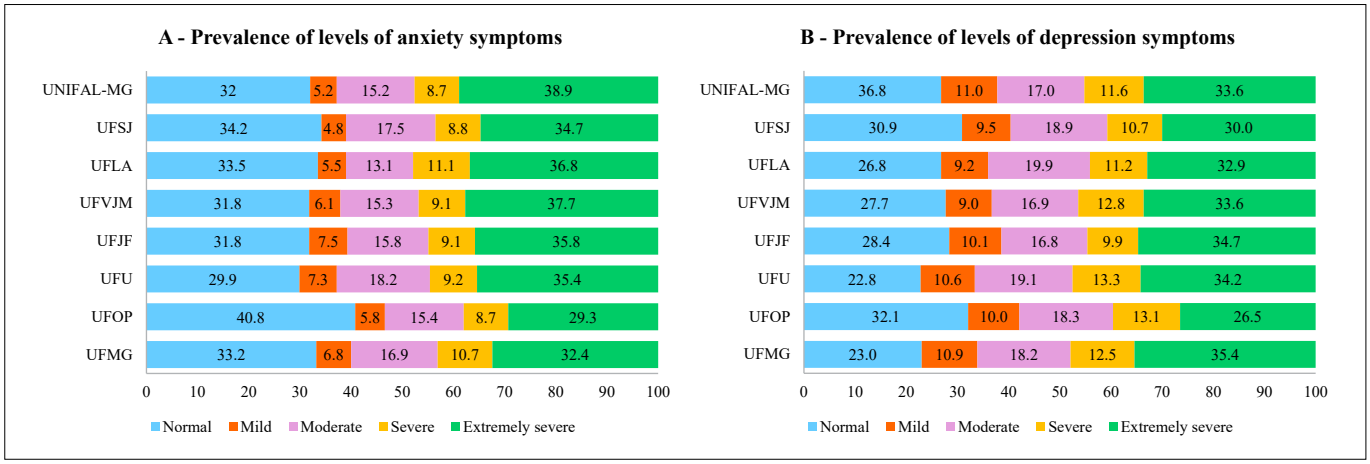


Figure 3. Prevalence of symptoms of anxiety and depression in university students, according to participating federal institutions of higher education. Project on Anxiety and Depression in University Students, 2021–2022 (n = 8,650).

This scenario may be understandable, considering the magnitude of changes in academic routines owing to the inclusion of remote teaching.[47] However, universities play a fundamental role in supporting university students and in the development of public policies that focus on promoting mental health, as well as actions and strategies to better address the effects of the pandemic. In addition, considering that universities represent an opportune environment for health promotion, institutions should contribute to supporting networks and welcome counseling centers for students to share coping resources and encourage them to take measures to protect their mental health.[7]

The findings of this study have some limitations. First, the inherent limitation of the adopted design, owing to its cross-sectional nature, did not allow for an assessment of the impact of the pandemic on the occurrence of mental disorders. Another limitation is the non-probabilistic sample in which all students were invited to participate. Thus, the possibility of response bias was highlighted. Those with a previous diagnosis of a mental disorder or related difficulties were possibly more likely to participate in the study, which may have contributed to the overestimation of the prevalence of symptoms of mental disorders found in the present study. In addition, the presence of symptoms of anxiety and depression was measured using a self-reported scale that assesses the symptoms and is not based on a medical diagnosis of the disease. The stratification of the classifications adopted in this study may differ from those adopted by other authors in national and international studies. Furthermore, different measurement tools and cut-off points have been used to assess the presence of symptoms of anxiety and depression, which may have influenced the comparison of the studies presented here. Although the results indicated a high prevalence of mental disorders among students, interpretation and comparison with other studies should be conducted with caution.

Despite these limitations, this study has strengths and expands the scientific knowledge about mental disorders among university students during the COVID-19 pandemic. It was conducted with a large sample of university students from eight public institutions of higher education, and the findings presented must be considered at both the state and local levels so that actions for the protection, control, and reduction of mental disorders can be targets for sustainable and effective policies in the university population.

CONCLUSION

The results showed a high prevalence of symptoms of anxiety and depression among students during the suspension of face-to-face activities in universities. Thus, together with other findings in the literature, this study adds relevant evidence to guide more cost-effective actions toward priority groups, in addition to providing evidence of possible damages resulting from the pandemic that require attention, as they may have short- and long-term consequences. Furthermore, considering that universities represent an opportune environment for promoting health, institutions must create actions such as psychological counseling services and support groups as well as develop policies that support diversity and inclusion aimed at the physical and mental well-being of students.

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Patients with DVT and primary antiphospholipid syndrome have worse obstetric outcomes than pregnant women with DVT and negative antiphospholipid antibodies: a retrospective cohort study

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ABSTRACT

BACKGROUND: Pregnant women are at an increased risk of thromboembolism compared with non-pregnant women. Venous thrombosis is a manifestation of antiphospholipid syndrome (APS), an autoimmune thrombophilia associated with pregnancy morbidity.

OBJECTIVES: This study was designed to compare gestational outcomes of pregnant patients with deep venous thrombosis (DVT) and primary APS with outcomes of patients with DVT and negative results for antiphospholipid antibodies (aPLs).

DESIGN AND SETTING: This was a retrospective cohort study with data collected from patients with DVT who received prenatal care for autoimmunity and thrombophilia at Hospital Universitário Pedro Ernesto, Rio de Janeiro.

METHODS: All patients with DVT were tested for aPLs. Those with positive results were tested again after 12 weeks and classified as having primary APS. Patients with systemic lupus erythematosus, superficial venous thrombosis without DVT, twin pregnancies, or fetuses with congenital malformations were excluded.

RESULTS: This study included 171 patients (39 with APS, 132 with DVT and negative aPL results). Patients with primary APS and DVT had higher frequencies of miscarriages ($P = 0.004$) and stillbirths during previous pregnancies ($P < 0.001$). When obstetric outcomes were analyzed prospectively, APS patients had a lower birth weight ($P = 0.001$) and higher rates of oligohydramnios ($P = 0.04$), intrauterine growth restriction ($P = 0.01$), preeclampsia ($P = 0.04$), stillbirths ($P = 0.02$), and small-for-gestational-age newborns ($P < 0.001$) than patients with DVT and negative aPL results. The latter group had gestational outcomes similar to those of the general population.

CONCLUSIONS: Patients with primary APS have adverse obstetric outcomes despite appropriate treatment, whereas those with DVT and negative for aPLs have favorable results.

INTRODUCTION

Pregnant women have four times the risk of thromboembolism compared with non-pregnant women.[1] Among other risk factors, pregnancy is a hypercoagulable condition preparatory to childbirth, and compression of the inferior vena cava by the gravid uterus contributes to venous stasis, thus favoring thrombotic phenomena.[1]

Venous thrombosis is a manifestation of antiphospholipid syndrome (APS), an autoimmune disease associated with vascular manifestations and circulating antiphospholipid antibodies (aPLs). It is estimated that the overall aPL frequency in patients with deep venous thrombosis (DVT) is 9.5% and, as approximately 70% of individuals with APS are female, this disease is found in women of reproductive age.[2]

Pregnancy morbidity is also a well-recognized presentation of APS and is part of the classification criteria.[3] Women with persistent aPLs have a higher incidence of recurrent abortions, fetal losses, preeclampsia (PE), and placental insufficiency than the general population.[3] These events were also previously associated with hereditary thrombophilias; however, recent literature questions whether this relationship really exists.[4]

OBJECTIVES

This study aimed to compare the gestational outcomes of pregnant patients with a history of or current DVT and primary APS with outcomes of patients with DVT and negative results for aPLs.

METHODS

This was a cohort study with retrospective data collection of patients with DVT that occurred before or during pregnancy, who received prenatal care for autoimmunity and thrombophilia at Hospital Universitário Pedro Ernesto, Rio de Janeiro, since 2005. All patients had DVT as an entry criterion and were tested for aPLs at least once, while patients with positive aPL results were retested after 12 weeks to confirm primary APS classification.[3] Patients were not routinely tested for inherited thrombophilia as it would not change the recommended treatment according to current protocols. Patients with systemic lupus erythematosus, superficial venous thrombosis without DVT, twin pregnancies, or fetuses with congenital malformations were excluded from the analysis.

Clinical manifestations, demographic and obstetric characteristics, gestational results, and prescribed treatments were organized in tables and subsequently submitted for descriptive statistical analysis. Fisher's exact test was used to compare categorical variables, and the Mann–Whitney U test was used for continuous variables that did not show a normal distribution. This study was approved by the local institutional Ethics Committee of Hospital Universitário Pedro Ernesto, Rio de Janeiro (approval number: 02190912.6.1001.5259).

RESULTS

One hundred eighty-five pregnancies in 171 patients with a history of DVT were evaluated. Of these, 39 fulfilled the APS criteria (Group 1) and 132 were aPL-negative (Group 2). Patients with APS had a higher mean age (32.4 ± 5.2 versus 29.6 ± 6.4, P = 0.006) and more previous stillbirths (23% versus 2%, P < 0.001) and miscarriages (43.5% versus 20.45%, P = 0.004) (**Table 1**). Another issue identified was the diagnosis of thrombosis (7.6% versus 21.2%, P = 0.02) during this pregnancy. Among the comorbidities, the more frequent were systemic arterial hypertension (7.6% versus 86%, P = 0.3), type 2 diabetes (5.1% versus 3.0%, P = 0.2), and gestational diabetes (5.1% vs. 7.5%, P = 0.3). Among patients with DVT, 9.8% had already received treatment (full-dose anticoagulation) at the beginning of pregnancy.

The most frequent autoantibody in Group 1 was lupus anticoagulant (56%), with three triple-positive patients. In both groups, the most common site of DVT was the lower limbs (82% and 90.1%, respectively). All patients in Group 1 used anticoagulants during pregnancy, with a predominance of full anticoagulation (89.7%, P < 0.001), and 82% used low dose aspirin (LDA), while 61.3% of Group 2 used prophylactic anticoagulants (P < 0.001), and 57.5% used LDA (P = 0.003).

Among adverse obstetric outcomes, patients with APS had worse gestational results (**Table 2**), such as higher rates of oligohydramnios (10.2% versus 2.2%, P = 0.04), PE (15.3% versus 5.3%, P = 0.04), and intrauterine growth restriction (IUGR) (17.9% versus 5.3%, P = 0.04), and lower birthweight (2,877 g ± 548 versus 3,225 g ± 565, P = 0.001) when compared with aPL-negative patients. Two cases of intrauterine fetal death occurred in the APS group. There were no differences between the two groups in terms of the route of delivery, 5 min Apgar score, admission to the neonatal intensive care unit, and premature delivery.

DISCUSSION

Obstetric complications such as fetal death, preterm birth, PE, and recurrent early miscarriage (REM) are characteristic manifestations of APS. These complications can occur in patients with known APS with previous arterial or venous events in any tissue or organ, or they can be the first and only manifestations. Pregnancy in patients with APS is considered high risk and requires careful prenatal clinical follow-up, eliminating or minimizing concomitant thrombotic risk factors.[5]

The current recommended treatment for APS patients and vascular thrombosis is LDA plus full-dose heparin throughout pregnancy.[5] Although treatment can significantly improve live birth rates, the frequency of adverse obstetric outcomes and even pregnancy loss remains high.[1] In this scenario, there is no study to support the use of any different drug, and proposed treatments rely on expert opinion. New pathogenic mechanisms of aPL-mediated pregnancy loss have been investigated in recent years, and this may be helpful in finding specific targets for future treatment proposals for refractory cases.[6] The main question is whether the treatment can prevent the development of PE and intrauterine growth restriction in aPL-positive patients.

The actual frequency of PE in treated APS patients is still unknown, but there are reports ranging from 14% to as high as 50%, with half of the cases being severe. This rate is considerably higher than that seen in the general population, estimated up to 7%.[6] In this study, 15% of APS patients developed PE, despite the fact that more than 80% used LDA. On the other hand, patients with DVT and negative aPL results developed PE in 5.3% of pregnancies, a frequency that is similar to that reported in Brazil.[7]

This high frequency, despite treatment, may represent a different pathway than that of non-aPL-related hypertensive disorders of pregnancy. For example, LDA, recommended as standard-of-care for APS during pregnancy, reduced the occurrence of PE in 53% of non-APS high-risk patients when started before 16 weeks of pregnancy, with a reduction of almost 80% in severe cases.[8]

Table 1. Characteristics of patients with DVT who received prenatal care for autoimmunity and thrombophilia at Hospital Universitário Pedro Ernesto, Rio de Janeiro

Variable	PAPS (n = 39)	aPL negative (n = 132)	P value
Age at birth (years)			
Mean ± SD	32.4 ± 5.2	29.6 ± 6.4	**0.006**
Min–Max	21–42	15–44	
Abortion history			
N (%)	17 (43.5%)	27 (20.45%)	**0.004**
Background of stillbirth			
N (%)	9 (23%)	2 (1.5%)	**0.00002**
Trombosis in current pregnancy			
N (%)	3 (7.6%)	28 (21.2%)	0.02
Comorbidities			
Arterial Hypertension	3 (7.6%)	8 (6%)	0.3
Type 2 Diabetes	2 (5.1%)	4 (3%)	0.2
Gestational Diabetes	2 (5.1%)	10 (7.5%)	0.3
Others	4 (10.2%)	5 (3.7%)	0.07
DVT			
Lower limbs	32 (82%)	119 (90.1%)	0.1
Chronic PE	1 (2.5%)	3 (2.2%)	0.6
Other locations	6 (15.3%)	13 (9.8%)	0.1
Immunological profile	N		
LAC	22 (56%)	N/A	
ACL			
IgM	5 (12.8%)	N/A	
IgG	11 (28.2%)	N/A	
AntiB2			
IgM	3 (7.6%)	N/A	
IgG	6 (15.3%)	N/A	
Treatment			
Aspirin use (with or without anticoagulant)	32 (82%)	76 (57.5%)	**0.003**
No anticoagulant	0	8 (6%)	0.06
Prophylatic anticoagulant only	2 (5.1%)	31 (23.4%)	**0.003**
Prophylatic anticoagulant plus aspirin	2 (5.1%)	50 (37.8%)	**< 0.0001**
Full-dose anticoagulant only	5 (12.8%)	22 (16.6%)	0.29
Full-dose anticoagulant plus Aspirin	30 (76.9%)	21 (15.9%)	**< 0.0001**

PAPS: primary antiphospholipid syndrome; aPL: antiphospholipid antibody; DVT: deep venous thrombosis; N/A: not applicable.

While studies in APS patients are still lacking, we do not seem to be closer to those numbers with current treatment.

IUGR is another placenta-mediated event associated with APS. An accurate diagnosis for this condition is still lacking in the obstetric field, but the usual definition is based on estimated fetal weight below the 10th percentile.[9] The described rate of IUGR in APS patients varies from 15% to 21% in the literature, which is similar to our findings, but there are reports of almost 40% of small for gestational age neonates in patients with thrombotic APS.[6] In addition to PE, IUGR is commonly found in pregnant women with APS before and after treatment. Both diseases represent different clinical manifestations of abnormal placental function and can occur in the same patient. However, isolated fetal impairment is possible and may develop with absent or minimal maternal signs, such as a small uterine height. Therefore, it is recommended that monthly ultrasound evaluation and Doppler velocimetry studies be performed routinely for APS patients, starting after 26 weeks of pregnancy.[5]

Again, the treatment for this presentation of obstetric APS is disappointing. In this study, pregnant patients with APS had more IUGR and newborns with lower birthweight than aPL-negative patients. Our results are similar to those of previous studies that evaluated obstetric outcomes in APS patients and demonstrated the difficulty in reducing pregnancy morbidity in this group.[10]

It is also important to note that preterm birth is the most frequent neonatal complication of APS during pregnancy, affecting between 20% and 25% of patients,[6] and is mainly caused by medical intervention because of PE and/or IUGR. Preterm delivery is required in approximately one-third of APS patients with PE,[6] while spontaneous premature birth is less frequent. In this study,

Table 2. Details of delivery, newborns, and adverse obstetric outcomes of patients with DVT

Variable	PAPS (n = 39)		aPL negative (n = 132)		P value
Delivery	n	%	n	%	P
Vaginal	13	33.3	59	44.6	0,1
C-section	26	66.6	73	55.3	0.1
Gestational age (weeks)	n = 37*				
Mean ± SD	37.6 ± 1.5		38.1 ± 1.7		0.08
Newborn weight	n = 37*				
Mean ± SD	2877 ± 548		3225 ± 565		0.001
Small for gestational age	n = 37*				
	7	18.9%	6	4.5%	0.008
5 min Apgar score	n = 37*				
	8.9	± 1.1	8.8	± 0.7	0.6
Admission to NICU	n = 37*				
	5	13.5%	16	12.1%	0.5
Oligohydramnios	4	10.2	3	2.2	0.04
Intrauterine growth restriction	7	17.9	7	5.3	0.01
Premature rupture of membranes	3	7.6	17	12.8	0.2
Preeclampsia	6	15.3	7	5.3	0.04
Premature delivery	7	17.9	15	11.3	0.2
Stillbirth and neonatal death	2	5.1	0	–	0.02
Acute fetal distress	7	17.9	13	9.8	0.1

DVT: deep venous thrombosis; PAPS: primary antiphospholipid syndrome; aPL: antiphospholipid antibody; NICU: neonatal intensive care unit; * Two stillbirths were excluded.

the patients with APS had a higher number of preterm births; however, the difference was not statistically significant. As the frequencies of PE and IUGR remain high in women with APS, it is difficult to determine an exact estimate of spontaneous preterm births in these patients. Specific treatment to prevent premature birth is not recommended as it is a common consequence of other obstetric complications.

In addition to APS, hereditary thrombophilia is another common cause of DVT. This type of thrombophilia is defined as the tendency for thrombosis due to hereditary alterations (protein C, S, and antithrombin deficiencies; factor V Leiden; and prothrombin gene mutations). There are inconsistent associations of this group with recurrent pregnancy loss or stillbirth, and the American College of Obstetricians and Gynecologists (ACOG) argues that the prophylactic dose treatment of LMWH to improve live birth rates in women with hereditary thrombophilia and a history of pregnancy loss shows no benefit when compared to no treatment.[4]

Similarly, the ACOG does not recommend screening for hereditary thrombophilia in women who have obstetric complications, including REM, placental abruption, IUGR, or PE, because it is unclear whether anticoagulation reduces the recurrence of these events.[4] In this study, the rates of PE and preterm births in patients with DVT and negative aPL results were 5.3% and 11.3%, which were similar to those of the Brazilian general population,[7] and the mean birth weight was 3.225 g (± 565). The results demonstrated that these patients had a favorable gestational prognosis that did not differ significantly from that of low-risk pregnancies.

One of the limitations of this study is the difficulty in reproducing the study in other locations, since it was carried out at a single center. The retrospective nature of the study could also lead to data loss in medical records. In addition, the absence of a control group of pregnant women without any diseases and the possibility of testing antibodies during pregnancy may lead to false-negative results.

However, this study was conducted in a specialized high-risk prenatal center with a large number of patients with venous thrombosis with and without APS, forming a homogeneous population despite its rarity. To reduce confounding factors, patients with systemic lupus erythematosus were excluded, allowing for a clearer analysis of the impact of primary APS on pregnancy.

CONCLUSIONS

The presence of aPLs in patients with a history of DVT is associated with worse pregnancy outcomes, whereas patients with venous thrombosis and negative aPL results have gestational results similar to those in the general population. Our study suggests that investigation for APS is important for adequate follow-up of pregnant women with a history of DVT. Furthermore, the treatment of patients with APS during pregnancy can significantly improve live birth rates; however, other obstetric complications, such as PE, IUGR, and low birthweight, remain high despite treatment.

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Prevalence and factors associated with actinic keratosis in 1346 patients attending at a public dermatology service: a cross-sectional study

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ABSTRACT

BACKGROUND: Actinic keratosis is a common preneoplastic dermatosis and is the third most common reason for dermatological consultations. Identifying the associated factors, diagnosis, and early treatment of actinic keratosis are crucial for reducing the risk of developing skin cancer and costs to the healthcare system.

OBJECTIVE: To evaluate the prevalence and factors associated with actinic keratosis in individuals treated at a public dermatology service.

DESIGN AND SETTING: A cross-sectional observational study was conducted with 1346 patients treated by a public dermatology service.

METHODS: The demographic and dermatological characteristics of patients were recorded. The presence of actinic keratosis was determined by clinical dermatological identification.

RESULTS: Most participants were elderly, white, and exposed to the sun without protection or during occupational activity. The evolution time of cutaneous lesions was <1 year in 46.8% of participants. Actinic keratosis was the most common skin lesion, being present in 29.3% of participants. The main approach adopted was cryotherapy. Keratosis was associated with white skin color, elderly age, personal and family history of skin cancer, exposure to the sun without protection at work, and limb involvement. When the associated factors were analyzed using a regression model, skin color and affected body segments were the main predictors of actinic keratosis.

CONCLUSION: The prevalence of actinic keratosis was 29.3%, being higher in people with fair skin, more than two affected segments, skin lesions on the limbs, older age, and unprotected sun exposure. These indicators are important for supporting decision-making and contributing to improving public policies.

INTRODUCTION

Actinic keratosis is a common preneoplastic dermatosis. In Brazil, actinic keratosis represents the fourth most common dermatological diagnosis, only behind acne, photoaging, and non-melanoma skin cancer. Among individuals aged > 65 years, actinic keratosis is the primary reason for attending a dermatologist.[1]

Due to its potential to develop into skin cancer, actinic keratosis is of significant importance, given that skin neoplasia is considered a serious public health problem, with a high incidence and impact on the lives of the affected population.[2] Some public policies have been created to reduce the incidence of cancer and improve quality of life. However, the considerable challenge and difficulty in accessing diagnostic services, among other problems, weaken these policies.[3]

Studies on actinic dermatosis in Brazil and specific public policies for skin cancer are scarce. With this, epidemiology has emerged as an important ally, providing local diagnosis and information for the development of more efficient, effective, and equitable management models.[4]

Cross-sectional studies assist in the critical thinking process aimed at identifying recognition, prevention, and treatment strategies. Considering the importance of deepening studies on actinic keratosis, this study sought to improve discussions on the subject, support decision-making by responsible bodies and the population, and improve public policies.

OBJECTIVE

To evaluate the prevalence and factors associated with actinic keratosis in 1,346 individuals treated at a public dermatology service.

METHODS

This was an epidemiological, observational, cross-sectional study with retrospective data collection approved by the CAAE Research Ethics Committee (51477421200005065) on November 30, 2021. This study was conducted in accordance with the recommendations of *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE), as described by the STROBE *checklist* to guide the writing of cross-sectional observational studies.[5]

The sample size was obtained by convenience and comprised all people treated in 2019 at a public dermatology reference center, with 1,409 eligible individuals. The inclusion criteria were as follows: patients of both sexes who were treated at that service in 2019, had medical records, and were aged 18 years or older. Patients with incomplete or illegible medical records were excluded. After applying the aforementioned criteria, 1,346 individuals were included in this study.

Data were collected by analyzing medical records written manually by the service team. The following variables were used to characterize the demographic profile: sex, age group, color, history of cancer, family history of skin cancer, sun exposure, and reason for sun exposure. The dermatological profile included clinical diagnosis, number of diagnoses, location, number of affected areas, therapeutic approach, and evolution time of skin lesions.

The presence or absence of actinic keratosis (i.e., the dependent variable) was determined through clinical dermatological identification based on the following aspects: lesions with an erythematous background and rough appearance, sometimes with scaling, in regions exposed to the sun.[6]

Dermoscopic examination was performed as necessary for differential diagnosis, considering actinic keratosis with the following aspects: erythema that forms a pinkish-reddish pseudo-vascular network that surrounds hair follicles; yellowish-white scales; thin wavy vessels that surround the follicles; and follicular openings filled with yellowish keratotic plugs.[6]

Finally, records regarding the proposed treatment (cryotherapy, surgery, appointment at the service, or referral to another service) were collected to identify the conduct in relation to the dermatological diagnosis.

Descriptive analyses of the data were performed using absolute and relative frequencies. Bivariate inferential analysis associating the presence or absence of actinic keratosis with independent variables was performed using the chi-square test. A generalized linear model with a binary logistic link function was used to verify the predictor variables of actinic keratosis and prevalence rates. Variables with $P < 0.2$ in the bivariate analysis were included in the model. Statistical analysis was performed using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA), and a significance level of 5% ($P \leq 0.05$) was adopted for all analyses.

RESULTS

The study population comprised mostly elderly (64.6%), female (60.1%), and white (73.5%) individuals. Of these, 34% had a history of cancer, and 36.4% reported cases of skin cancer in the family. Most participants were exposed to the sun without protection (74.4%), mainly because of work (**Table 1**).

Dermatological diagnoses and treatment profiles are presented in **Table 2**. The presence of actinic keratosis was recorded in 29.3% of samples, indicating its high frequency in the studied population. Actinic keratosis was the most frequent dermatological diagnosis, followed by basal cell and spinocellular carcinomas. Most lesions were recent (less than a year old); lesions were located in the cephalic segment in more than half of the cases. Surgery, cryotherapy, and guidance stood out among the most widely adopted therapeutic approaches in the studied locations.

Regarding the association between the demographic profile and the presence of actinic keratosis, a statistically significant difference was found in white individuals ($P < 0.001$) aged > 60 years ($P < 0.001$) who were exposed to the sun without protection ($P = 0.001$) for professional reasons and had a personal ($P< 0.001$) and family ($P = 0.003$) history of skin cancer (**Table 3**).

Table 4 presents the relationship between actinic keratosis and dermatological profile, revealing the association of actinic keratosis with location on the limbs ($P < 0.001$) and two or three affected sites ($P < 0.001$). The most commonly adopted approaches for keratosis were cryotherapy and formula.

When the variables were inserted into a regression model to investigate the predictive factors for actinic keratosis (**Table 5**), the prevalence of actinic keratosis was found to be higher in people with fair skin (300%), more than two affected segments (211%),

Table 1. Demographic profile of patients treated by a public dermatology service in 2019

Variables	n = 1346 (%)
Female sex	809 (60.1)
Age range	
Adult	467 (34.3)
Elderly	879 (64.6)
Skin color	
White	989 (73.5)
Brown/black	357 (26.5)
Cancer history	458 (34)
Family history of skin cancer	490 (36.4)
Sun exposure	
Did not expose themselves	90 (6.7)
Unprotected exposure	1002 (74.4)
Protected exposure	254 (18.9)
Reason for sun exposure, n = 1256	
Leisure	428 (34.1)
Professional	547 (43.5)
Both	281 (22.4)

Table 2. Dermatological profile and procedures adopted in the face of diagnosis in patients treated by a public dermatology service in 2019

Variables	n = 1346 (%)
Clinical diagnosis	
Actinic keratosis	395 (29.3)
Basal cell carcinoma	327 (24.3)
Squamous cell carcinoma	49 (3.6)
Melanoma	9 (0.7)
Other malignant tumors	11 (0.8)
Other dermatoses	493 (36.6)
Absence of dermatoses	132 (9.7)
Location of the injury	
Head	797 (59.2)
Stem	373 (27.7)
Limbs	620 (46.1)
Number of affected locations (n = 1345)	
One location	956 (71)
Two locations	307 (22.8)
Three or more locations	82 (6.1)
Evolution time of lesions	
<1 year	630 (46.8)
1–3 years	393 (29.2)
>3 years	323 (24)
Conduct	
Guidance	455 (33.8)
Surgery	379 (28.2)
Cryotherapy	294 (21.8)
Biopsy	35 (2.6)
Electrocauterization	21 (1.6)
Formula	19 (1.4)

Table 3. Association of actinic keratosis with the demographic profile of patients treated by a public dermatology service in 2019

Variables	Actinic keratosis		
	No n = 951 (70.7%)	Yes n = 395 (29.3%)	P
Sex			
Female	585 (61.5)	224 (56.7)	0.101[a]
Male	366 (38.5)	171 (43.3)	
Skin color			
White	639 (67.2)	**350 (88.6)**[b]	**< 0.001***,[a]
Brown/black	**312 (32.8)**[b]	45 (11.4)	
Age range			
Adults	**376 (39.5)**[b]	91 (23)	**< 0.001***,[a]
Elderly	575 (60.5)	**304 (77)**[b]	
Skin cancer history	290 (30.5)	**168 (42.5)**[b]	**< 0.001***,[a]
Family history of skin cancer	322 (33.9)	**168 (42.5)**[b]	**0.003***,[a]
Exhibition			
Without protection	691 (71.6)	**318 (80.5)**[b]	**0.001***, [a]
With protection	**196 (20.3)**[b]	61 (15.4)	
Did not expose themselves	**78 (8.1)**[b]	16 (4.1)	
Exposure ratio, n = 1256			
Leisure	**322 (36.7)**[b]	106(28)	**< 0.001***,[a]
Professional	348 (39.7)	**199 (52.5)**[b]	
Both	207 (23.6)	74 (19.5)	

* P ≤ 0.05; [a] Pearson's chi-square; [b] adjusted residual > 1.96.

skin lesions on the limbs (186%), older age (177%), and unprotected sun exposure (137%) than in those without keratosis (P < 0.05).

DISCUSSION

With the global increase in life expectancy, the number of individuals with actinic keratosis is estimated to also increase.[7] In countries such as Australia, for example, the prevalence is approximately 40%.[8] In Austria, one study reported a prevalence of 31% in patients aged > 30 years.[9] In this study, actinic keratosis was present in 29% of the studied sample, approaching global statistics.

Skin cancer represents the most common type of cancer in Brazil, with a rate of 223.6 per 100,000 inhabitants.[10] In 2023, approximately 229,000 cases of skin cancer were detected in the Brazilian population.[10] Considering that actinic keratosis is a precancerous lesion, the high prevalence found in this study is an important public health problem.

Injury is significantly associated with older age and can be explained by the longer period of sun exposure in this population, as age is an independent risk factor for the development of sun-related injuries.[7,11]

Skin neoplasms are also more common in light-skinned individuals, who are inadvertently exposed to the sun during childhood and adolescence.[11] Our findings corroborate this statement; the white population corresponded to 73.1% of the cases analyzed, with a significant association for the presence of actinic keratosis.

Due to aesthetic and cultural demands, women seek health services more frequently and earlier, enabling diagnosis and treatment in the early stages of the disease.[6] This fact explains the greater frequency of women in the dermatological program, albeit without a statistical association with actinic keratosis.

Just over one-third of the population analyzed (33.7%) already had some form of skin cancer. More recent studies have demonstrated that 50% of those who have had a basal cell skin cancer subtype will have another within 5 years after diagnosis.[11] Regarding the history of skin cancer in the family, there is a tendency for this ratio to increase each year.[1]

In 2013, the National Policy for Cancer Prevention and Control was established to reduce the incidence of cancer and improve the quality of life of patients with cancer. The policy aims to promote the prevention, early diagnosis, and timely treatment of this condition.[12] However, there have been great challenges, including the difficulty in accessing diagnostic services due to the availability of services, equipment, and geographic location, as well as the delay in carrying out consultations and examinations necessary for diagnosis.[12]

Table 4. Association of actinic keratosis with he dermatological profile of patients treated by a public dermatology service in 2019

Variables	Actinic keratosis		
	No n = 951 (70.7%)	Yes n = 395 (29.3%)	P
Clinical diagnosis			
Melanoma	8 (0.8)	1 (0.3)	0.402[b,*]
Squamous cell carcinoma	**41 (4.3)**	8 (2)	**0.041[a,*]**
Basal cell carcinoma	**277 (29.1)** [c]	50 (12.7)	**< 0.001[*,a]**
Other malignant tumors	12 (1.3)	2 (0.5)	0.213[b,*]
Location			
Head	554 (58.3)	243 (61.5)	0.267[a]
Stem	256 (26.9)	117 (29.6)	0.313[a]
Limbs	369 (38.8)	**251 (63.5)** [c]	**< 0.001[*,a]**
Number of affected locations (n = 1345)			
One location	**746 (78.4)** [c]	210 (53.3)	
Two locations	165 (17.4)	**142 (36)** [c]	**< 0.001[*,a]**
Three or more locations	40 (4.2)	**42 (10.7)** [c]	
Evolution time of lesions			
<1 year	450 (47.3)	180 (45.6)	
1–3 years	263 (27.7)	130 (32.9)	0.119
>3 years	238 (25)	85 (24)	
Conduct			
Guidance	**409 (43.0)** [c]	46 (11.6)	**< 0.001[*,a]**
Surgery	267 (28.1)	112 (28.4)	0.918[a]
Cryotherapy	88 (9.3)	**206 (52.2)** [c]	**< 0.001[*,a]**
Biopsy	**30 (3.2)**	5 (1.3)	**0.047[*,a]**
Electrocauterization	13 (1.4)	8 (2)	0.375[a]
Formula	5 (0.5)	**14 (3.5)** [c]	**< 0.001[*,a]**

*P < 0.05; [a] Pearson's chi-square; [b] Fisher-Freeman exact; [c] adjusted residual > 1.96.

Table 5. Predictor variables associated with actinic keratosis and the respective prevalence ratios according to logistic regression analysis

Variables	P value	PR	95% CI	
			Bottom	Higher
Light skin	< 0.001	3,077	2,167	4,369
Elderly	< 0.001	1,777	1,336	2,365
Unprotected sun exposure	0.043	1,373	1,011	1,866
>2 segments affected	< 0.001	2,119	1,562	2,873
Skin lesions on limbs	< 0.001	1,867	1,407	2,477

PR = prevalence ratio; CI = confidence interval.

Unprotected sun exposure showed a statistically significant association with the presence of actinic keratosis, which may reflect a lack of population guidance regarding the risks of sun exposure. In a study conducted in Mato Grosso do Sul, more than half of the participants never used chemical photoprotection (65%); among those who used chemical photoprotection, 57.1% did not reapply the product during the day.[13]

Healthcare professionals have the duty to promote health education and communicate with the population through easy and understandable language while envisioning the exchange of information between individuals, respecting the individuality and peculiarities of each one, and enabling health promotion through educational practices. This is the most efficient method to promote health and guide healthy lifestyle practices. This process can be conducted anywhere and at any time, mainly during campaign events, in schools, in environments with greater sun exposure (e.g., beaches and clubs), and in health units through primary care.[14]

The evolution time of skin lesions was < 1 year in most samples. With respect to actinic keratosis, time is decisive for its progression to invasive squamous cell carcinoma (SCC); the longer the time without treatment, the greater the probability of progression to invasion. At 1 year of evolution, the rate of conversion of lesions to malignancy ranges from approximately 0.25% to 20%; however, some lesions remain stable throughout their evolution, which can last for > 3 years.[15]

Patients with multiple lesions caused by sun exposure have areas or fields of cancerization and regions of skin that apparently do not have lesions identified as neoplastic or preneoplastic, but are around those with this denomination. Attention should be paid to these areas, as cellular genetic material may have already been modified by UV rays.[16] This fact draws attention when analyzing **Table 4**. Of the 365 patients who had actinic keratosis, 61 (12.7%) also had other skin lesions, especially basal cell carcinomas.

It is known that the risk of developing SCC and basal cell carcinoma is greater than that in the general population.[17] An international population-based study showed that the probability of patients with actinic keratosis to develop skin cancer was six times higher than that in patients without actinic keratosis.[17] However, SCC was present in only 2% of patients, contradicting research that dictates the transformation of actinic keratosis into SCC.[17-19]

Actinic keratosis is preferentially located in areas exposed to the sun, such as the face, head, neck, neck, shoulders, forearms, and back of the hands, representing 75% of lesions.[20] These data are consistent with the results of our study, as head injuries accounted for 50% of injuries treated by the service, increasing to 61.5% in the presence of actinic keratosis.

Furthermore, injury was significantly associated with upper-limb involvement. The population, especially the rural population, works with hats and shirts, which act as physical protective barriers against UV rays but neglect areas such as arms, forearms, and hands.[21]

It is important to highlight that Law 4,027 of 2012 guides the provision of sunscreen as personal protective equipment, which is often not carried out by employers.[22] Intensive sun protection is the first step in controlling the emergence of actinic keratosis; to eliminate the risk of skin cancer, the ultimate goal is to remove all lesions.[23]

Early diagnosis and treatment are important to minimize disease progression and severity. Patients are recommended to receive therapy that addresses both visible lesions and subclinical damage

(field of cancerization). Although more studies are needed, treating cancer in the field is known to improve long-term prognosis, reduce economic burden, and maximize aesthetic results.[23]

The choice of treatment depends on effectiveness, duration of use, adverse effects, and cost. For this purpose, topical drugs, photodynamic therapy, and ablative procedures are available, including dermabrasion, lasers, and chemical *peels*.[23] In this study, the main therapies for actinic keratosis were cryotherapy and surgery. Compared to patients without actinic keratosis, cryotherapy and topical formulations were significantly associated with patients with this lesion.

The high cost of these treatments is a problem that hinders public policies on access for patients with cancer. Low income, which contributes to low access to preventive and therapeutic measures, is a risk factor associated with the development of these injuries.[24] In two years, 9.6 million people joined the group of Brazilians living in poverty. Since the beginning of the historical series of the National Household Sample Survey, poverty has never been as high as in 2021.[25]

Procedures recommended to treat cancer, such as chemical *peels*, photodynamic therapy, lasers, and even topical 5-fluorouracil (5-FU), are not available in the public health system or supplementary healthcare. The National Commission for the Incorporation of Technologies into the Unified Health System (SUS, in Portuguese) incorporated photodynamic therapy into the SUS for the treatment of basal cell carcinoma without considering actinic keratosis and fields of cancerization.[26]

In clinical practice, cryotherapy, which involves the application of highly effective liquid nitrogen, is the first therapeutic modality chosen in the face of actinic keratosis, surpassing even surgery.[27] As it is a painful procedure, the application may not be feasible owing to its non-tolerability, in addition, cryotherapy does not promote the treatment of the field of cancerization, being restricted to circumstantial injuries.[6]

For home use, 5-FU is the main drug used to treat actinic keratosis. The area of the skin to be treated must not be larger than 500 cm^2. Despite not being provided by the Unified Health System, it has a low cost, making it accessible to a significant proportion of patients. Although **Table 4** does not specify the combination of treatments, combined therapy is an excellent modality with a greater therapeutic effect and better usefulness in recalcitrant disease. Therefore, future treatment of actinic keratosis is therapy directed at the lesion and therapy directed at the field of cancerization.[28]

Currently, the biggest barrier to the treatment of skin cancer and pre-cancer in Brazil is related to adequate treatment time, which is crucial for favorable outcomes. When there is negligence, the chances of a cure decrease and the need for invasive procedures and the emergence of metastases increase.[29] The public service studied, stands out for its simultaneous access to dermatological and plastic surgery services, without the need for long waits in different locations. The presence of community members contributes to the credibility of the program, as they help provide guidance on the signs and symptoms of skin cancer, thus becoming great promoters of the project.

Guidance was the primary conduct adopted (34%). Guiding patients about their injuries is fundamental for therapeutic success and prevention. Health education is an important means of increasing healthy behavioral practices as a principle of primary healthcare.[14] The National Policy for Popular Health Education assists in political strategies and in defining methods for transforming autonomy, participation, and social control, with a focus on popular health education and strengthening popular care practices.[12]

CONCLUSION

The prevalence of actinic keratosis in the study population was 29.3%. The presence of this type of lesion was associated with white skin color, elderly age, unprotected sun exposure, and location on the limbs.

Considering that actinic keratosis is a precursor lesion of skin cancer, creating specific public policies to address this issue is important, mainly because it is easily preventable, diagnosable, and treatable. There have been great technological advances in this area. However, access to cutting-edge treatment in public services is not a reality for the Brazilian population because of its high value. The main way to avoid spending excessively is to invest in preventive measures.

Therefore, enhancing primary care as a gateway for disease prevention, diagnosis, and treatment is important. Health education can strengthen participation and social control by focusing on popular education and care practices. This important tool will assist health professionals in educating them about risk factors, providing guidance on prevention, such as the use of sunscreen, recognizing suspicious lesions, favoring early diagnosis, and qualifying innovative therapies.

Specific public policies for skin cancer and its preneoplastic lesions are essential to the protocols of the Unified Health System. The State's responsibility for the loss of therapeutic opportunities and increase in morbidity and mortality is conditioned by the existence of a universal health service. This reaffirms the principle of universality, which governs the SUS and which, in reality of many users, is often not incorporated.

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Validation of the Pearlin Mastery Scale for unpaid caregivers of people living with dementia in Brazil: a methodological study

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ABSTRACT

BACKGROUND: Sense of mastery has been described in the literature as a psychological resource potentially associated with reduced caregiver burden. However, there are no validated instruments in the Brazilian context that allow the evaluation of the sense of mastery as a possible outcome of interventions aimed at supporting unpaid caregivers of people with dementia.

OBJECTIVE: To validate the construct of the Brazilian version of the Pearlin Mastery Scale among unpaid caregivers of people living with dementia.

DESIGN AND SETTING: This methodological study was conducted with 100 unpaid caregivers of people living with dementia, cared for at home, and who resided in Brazil.

METHODS: Evidence of validity was tested based on internal structure, reliability, and correlations with theoretically related constructs. Sociodemographic data on sense of mastery, burden, depressive symptoms, anxiety, and quality of life were collected.

RESULTS: Difficulties involving burden (80%), depressive symptoms (70%), anxiety (65%), and low quality of life (62%) were reported. Satisfactory measures of adjustment were found in the factor analysis; however, by removing two inversely scored items, these measures improved, resulting in a Cronbach's alpha of 0.75. Significant correlations were found between sense of mastery and burden scores ($\rho = -.56$), symptoms of depression ($\rho = -.57$), anxiety ($\rho = -.57$), and quality of life ($\rho = .64$).

CONCLUSION: Evidence of validity was found for the Pearlin Mastery Scale Brazilian version based on the internal structure, reliability, and correlations with theoretically related constructs, indicating that it is a suitable instrument for use in Brazil.

INTRODUCTION

A sense of mastery is a psychological coping mechanism that reflects an individual's self-perception of control over the circumstances that affect their life. Unlike constructs that fall under beliefs and attitudes, such as self-efficacy, mastery is a more global concept and does not apply to specific situations or tasks. People with a high mastery level cope better with chronic stressful experiences, representing a protective factor for mental and physical well-being.[1–4] Unpaid caregivers of people living with dementia can have positive experiences that represent gains during care-related activities, such as strengthening their sense of mastery. In other words, caregivers perceive that there are important psychological benefits to this experience. In addition to a greater sense of mastery, other positive psychological effects of caregiving already documented in the literature include an increase in optimism, satisfaction, self-esteem, self-efficacy, and resilience.[2,4–6] Some authors suggest that a high level of sense of mastery acts as an important psychological mechanism that can mitigate the effects of the burden generated by care activities.[3,6,7]

Considerations of the positive effects of care are relatively new. In general, researchers who have evaluated the effectiveness of caregiver support interventions have focused on verifying the reduction in the negative impacts of caregiving, such as burden, depression, and anxiety.[8,9] Thus, there is little information on the positive effects of the experience of caring for people living with dementia, such as a sense of mastery. These effects also need to be investigated, as they provide a different look at the ways in which interventions can make a difference in the lives of

caregivers.[10] However, instruments to assess the sense of mastery have not yet been adapted for use in Brazil. The Perlin Mastery Scale is an internationally recognized instrument, with multiple studies from various countries providing satisfactory evidence of its validity. It has also been effectively applied in research across diverse contexts and populations.[11–14] Therefore, the validation of this instrument would allow the evaluation of the sense of mastery in Brazil, as well as the integration of Brazilian information with international literature.

The Brazilian Pearlin Mastery Scale (PMS-BR) is a one-dimensional instrument comprising seven items, originally developed by Pearlin and Schooler in the 1970s for a study on stress and coping with a general population sample aged between 18 and 65 years.[1] Since then, the instrument has been used to assess the sense of mastery in studies that show evidence of the scale for research and practical implementation. In Brazil, translation and cultural adaptation of the PMS were conducted specifically for unpaid caregivers of people living with dementia.[3,13–15] Given this, it is essential to analyze the evidence of validity for the PMS-BR to determine whether it can effectively evaluate the outcomes of interventions and support programs for caregivers in Brazil. Based on these considerations, this study aimed to assess the construct validity of the PMS-BR through confirmatory factor analysis and to examine its reliability among unpaid caregivers of individuals living with dementia.

METHODS

Study design

This was a methodological study of construct validation through confirmatory factor analysis of the PMS-BR.[15] Methodological studies are focused on the analysis and validation of measurement instruments, ensuring that they are appropriate for the population and context in question. This study aimed to assess the structural validity of the PMS-BR and verify its psychometric properties (such as validity and reliability) to ensure its application in a Brazilian context. Data were collected between January 2023 and April 2023. This study is a branch of an umbrella project evaluating the effects of the iSupport-Brazil program on unpaid caregivers of people living with dementia in Brazil.[16]

Participants

This study used a convenience sample of 100 unpaid caregivers of people living with dementia from various regions of Brazil. The sample size resulted in a ratio of more than 14 participants per item of the instrument being analyzed, which is a commonly accepted sampling approach, typically ranging from 7 to 10 participants per item, ensuring that the instrument analysis would be reliable.[17]

Selection criteria

The participants were people aged ≥ 18 years, who considered themselves to be unpaid carers of people living with dementia, had been doing so for at least six months, residing in any location in Brazil, who cared for a person with a dementia diagnosis (self-report and Ascertaining Dementia Interview [AD8] score ≥ 2) and had access to a smartphone, computer or tablet with internet. In addition, only participants with scores above the minimum values established for at least two of the following three measures were included in the study: ≥ 4 points in the assessment of overall burden perception, or ≥ 3 points in the assessment of anxiety symptoms, or ≥ 3 points in the assessment of depression symptoms. Caregivers of people living in long-term care institutions were excluded. These criteria were defined based on the iSupport-Brazil umbrella project, of which this study is a part.

Recruitment and data collection

Participants were recruited through posters, flyers, social media (Instagram and Facebook), and partnerships with associations affiliated with the Brazilian Federation of Alzheimer's (Febraz), such as the Brazilian Alzheimer's Association (ABRAz), and researchers from higher education institutions and public health services across Brazil who promoted the study on their websites, social media, and bulletin boards within their institutions. Individuals interested in participating in the study completed an online pre-registration (via Google Forms), providing information such as full name, email address, and WhatsApp details. The researchers then contacted the participants and sent them a link to an online form (via Google Forms) regarding the study's eligibility criteria. Participants who met the criteria received another link to a different form (via Google Forms) for data collection. This form included information about the study and items of the Informed Consent Form. Once consent was obtained, the participants answered the study questions. The entire recruitment and data collection process was conducted online.

STUDY VARIABLES

Sociodemographic and care characteristics: sex, age, marital status, skin color, region of residence, education, relationship with the person in need of care, time working in the position in days/week and hours/day, and type of dementia.

PMS-BR: The PMS-BR is a one-dimensional instrument of seven items scored on Likert scales from "1 = strongly agree" to "4 = strongly disagree", using reverse coding for items 4 and 6 of the scale, which are worded positively. The total score varies between seven and 28 points; the higher the score, the greater the sense of mastery.

Perceived burden: For inclusion in the study, a single item was answered on general burden perceptions (on a 10-point

Likert scale): "On a scale from 1 to 10, where 1 means 'not burdened' and 10 means 'extremely burdened', how burdened do you feel?". The participants answered the Zarit Burden Interview (ZBI) questionnaire to assess the subjective burden related to caring for another person using 22 items scored on a Likert scale from 0 to 4 points. The total score ranges from zero to 88, with higher scores indicating a greater perception of burden.[18,19]

Depression and anxiety symptoms: The Hospital Anxiety and Depression Scale (HADS) was used,[20] and adapted with validity evidence for use in Brazil.[21] The scale has satisfactory performance for assessing anxiety and depression among the general population through 14 items (seven specific questions for each construct) scored on a Likert scale from 0 to 3 points.[22] Results above eight points indicate a possible/probable manifestation of symptoms of depression and anxiety.

Quality of life: The Quality of Life Alzheimer's Disease (QoL-AD) scale,[23] adapted and with evidence of validity for use in Brazil,[24] was used to assess the quality of life of unpaid caregivers who assisted people living with Alzheimer's disease. The instrument consists of 13 items rated on a four-point scale, with a score of 1 assigned to "bad" and a score of 4 to "excellent." The total score ranged from 13 to 52, with higher scores indicating better quality of life.[23]

DATA ANALYSIS

Confirmatory factor analysis (CFA) was carried out using MPLUS software version 6.12.0, using the mean and variance-adjusted weighted least squares (WLSMV) method, recommended for models with categorical indicators, and considering the existence of a single factor. The fit measures included the chi-squared test (χ^2), which compared the sample correlation matrix with the correlation matrix estimated under the model (in this case, lower values indicated a good fit); Bentler's Comparative Fit Index (CFI); the Tucker–Lewis Index (TLI); the Root Mean Square Error of Approximation (RMSEA); and the Weighted Root Mean Square Residual (WRMR). CFI and TLI values (≥ 0.95), RMSEA (< 0.07), and WRMR (< 1) values were adopted as model fit criteria.[25–29]

The other analyses were carried out using SAS, version 9.4, Cronbach's alpha was calculated to check the internal consistency of the instruments (satisfactory ≥ 0.7);[30] Spearman's coefficient to check the discriminant construct validity through the correlation between the PMS-BR scores and those of the ZBI and HADS; and the convergent analysis between the PMS-BR scores and the QoL-AD scores (considering that a correlation < 0.3 = weak; between 0.3 and 0.5 = moderate; > 0.5 = strong).[31] A 95% confidence interval was adopted, with statistical significance set at $P \leq 0.05$.

ETHICAL ASPECTS

This study was conducted in accordance with the guidelines of Resolutions No. 466/2012 and No. 510/2016 of the Brazilian National Health Council. This study was approved by the Human Research Ethics Committee of the Universidade Federal de São Carlos (Protocol No. 5.332.333; CAAE: 88157118.0.1001.5504).

RESULTS

Of the 100 caregivers who participated, 95% were female, with a mean age of 53.4 years (standard deviation: 9.32 years). Most of them were married (56%), self-declared as white (56%), and lived in the Southeast (65%). Around 90% reported ≥ 12 years of schooling, more than 85% reported being children of the person living with dementia, 40% had been caring for them for between 1 and 3 years, 67% were involved 6–7 days a week and 42% reported caring for 13 or more hours a day. More than 72% of participants reported that they cared for people with Alzheimer's disease. **Table 1** shows the descriptive statistics of the scores obtained for the measures of burden, depression, anxiety, and perceptions of quality of life.

Initially, although the adjustment measures were satisfactory in the CFA, the standardized factor loading estimate, which indicates the correlation of the variable with the instrument's single factor, showed lower factor loading values for items 4 and 6 of the

Table 1. Descriptive analysis of the measures of burden, depression, anxiety, and the participants' perceptions of quality of life (N* = 100). Brazil, 2023

Variable	*n*† (%) / *M*‡ (*SD*§)
ZBI‖	62.85 (12.6)
No burden (≤ 20)	5 (5%)
Light burden (21–40)	38 (38%)
Moderate to severe burden (41–60)	42 (42%)
Intense burden (≥ 61)	15 (15%)
HADS¶ – Overall score	18.72 (7.74)
HADS¶ – Depression	9.48 (3.77)
Possible/probable depression (≥ 8)	70 (70%)
No symptoms (≤ 7)	30 (30%)
HADS¶ – Anxiety	9.24 (4.31)
Possible/probable anxiety (≥ 8)	65 (65%)
No symptoms (≤ 7)	35 (35%)
QoL-AD – Overall score**	30.54 (7.5)
Higher levels (≥ 32)	38 (38%)
Lower levels (< 32)	62 (62%)

* N = total participants; † n = sample size; ‡ M = mean; § SD = standard deviation; ‖ ZBI = Zarit Burden Interview; ¶ HADS = Hospital Anxiety and Depression Scale; ** QoL-AD = Quality of Life-Alzheimer Disease.

scale (≤ 0.52), which are those scored inversely, in addition to item 6 not showing a significant correlation (**Table 2**).

On identifying this result, a new confirmatory factor analysis model without the inclusion of items 4 and 6 was tested and showed more satisfactory adjustment measures for all the indices, with a significant reduction in the RMSEA and chi-squared values, as well as an increase in the CFI and TLI values (**Table 3**).

By reducing the scale to five items, the internal consistency was increased from $\alpha = 0.73$ to $\alpha = 0.75$, reinforcing the more satisfactory validity evidence for the PMS-BR reduced version (**Table 4**).

There was a significant positive correlation of strong magnitude between PMS-BR scores and QoL-AD and a significant negative correlation of strong magnitude between the reduced version PMS-BR scores and ZBI, HADS—Depression, and HADS—Anxiety, establishing evidence for criterion validity based on correlations with theoretically related constructs using the PMS-BR reduced version in Brazil (**Table 5**).

DISCUSSION

In this study, evidence confirmed the expected unidimensional factor structure, significant correlations with related constructs, and reliability of the PMS-BR seven-item version. However, items 4 and 6 were excluded after finding evidence of a weak relationship between their scores and the factor score for this instrument. After excluding these items, the adjustment measures were more robust for the reduced version of the scale (five items), corroborating other studies,[3,12–14] which contributes to filling a gap in the lack of instruments to assess the important positive aspects involved in caring activities in Brazil.

Despite clear evidence of problems in the interpretation of items 4 and 6, the fit indices for the PMS-BR, the instrument's reliability, and the correlations with theoretically related constructs were satisfactory. However, it will be necessary to modify the wording of these items and conduct a new validity evidence assessment to determine whether the problem can be remedied. In general, low-magnitude correlations are found when there are different interpretations of the meaning of an item.

Table 4. Analysis of internal consistency between PMS-BR* items. Brazil, 2023

Item	Correlation between total score and item	Value of α if the item is excluded
1	0.508	0.687
2	0.474	0.693
3	0.525	0.68
4	0.443	0.7
5	0.544	0.677
6	0.161	0.764
7	0.485	0.69

* PMS-BR = Brazilian Pearlin Mastery Scale.

Table 2. Standardized factor loading estimates for each item. Brazil, 2023

	Estimate	Standard error	P value*
1. "I can't solve some of the problems I have"	0.65	0.061	< 0.001
2. "Sometimes I feel like I'm being forced to do things in life"	0.65	0.069	< 0.001
3. "I have little control over the things that happen to me"	0.69	0.072	< 0.001
4. "I can do anything when I put my mind to it"	0.52	0.076	< 0.001
5. "I often feel incapable of dealing with life's problems"	0.8	0.054	< 0.001
6. "How I deal with what happens to me in the future will depend mainly on me"	0.19	0.098	0.055
7. "For many important things in my life, there is little I can do to change them"	0.59	0.077	< 0.001

* P value = significance level.

Table 3. Results of the adjustment measures used for the PMS-BR AFC.*† Brazil, 2023

Adjustment index	Model – version 7 items	Model – version 5 items
RMSEA‡	0.071 (90% CI: 0–0.13)	0.047 (90% CI§: 0–0.153)
CFI‖	0.976	0.996
TLI¶	0.964	0.991
Chi-squared	21.146 (14)	6.104 (5)
WRMR**	0.579	0.372

* CFA = Confirmatory Factor Analysis; † PMS-BR = Brazilian Pearlin Mastery Scale; ‡ RMSEA = Root Mean Square Error of Approximation; § CI = Confidence Interval; ‖ CFI = Bentler's Comparative Fit Index; ¶ TLI = Tucker–Lewis Index; ** WRMR = Weighted Root Mean Square Residual.

Table 5. Analysis of criterion validity evidence. Brazil, 2023

		ZBI*	HADS† – Depression	HADS† – Anxiety	QoL-AD‡
PMS-BR	ρ§	−0.56	−0.57	−0.57	0.64
	p‖	< 0.01¶	< 0.01¶	< 0.01¶	< 0.01¶
	N**	100	100	100	100

* ZBI = Zarit Burden Interview; † HADS = Hospital Anxiety and Depression Scale; ‡ QoL-AD = Quality of Life-Alzheimer Disease; § ρ = Spearman's correlation coefficient; ‖ P value = Significance level; ¶ statistically significant value; ** N = Total participants.

In relation to the caregivers' profile, there was a large predominance of female participants in the sample (95%), with a mean age of 53 years, most of whom were white and married, which corroborates the National Report on Dementia in Brazil, which analyzed the context of Brazilian caregivers of people living with dementia and their main needs.[32] In addition, most of the participants had a high education level and worked as caregivers 6 to 7 days a week, for 13 or more hours a day. Despite changes in gender and cultural patterns, such as a reduction in fertility rates, an increase in education levels among women in the last three decades, and their entry into the labor market, the social responsibility that women assume for care activities is still notable.[33]

Analysis of the factor loadings for the PMS-BR items found a very low value for items 4 and 6 of the scale (≤ 0.52), corroborating the study carried out to develop the original version of the instrument, in which the authors carried out exploratory factor analysis, in which they observed reduced factor loadings for the items with inverse scores (≤ 0.47), but did not carry out reliability analysis.[1] In our analysis, the PMS-BR showed satisfactory internal consistency results through Cronbach's alpha, which showed a value of 0.73 for the full version and 0.75 for the five-item version (without those scored inversely).

A study of 392 family caregivers of dependent older adults in Singapore corroborated our findings with satisfactory reliability (0.8), which reflected a lower consistency for the two positively worded items. Without the two items, the analysis of the reduced version showed an acceptable model fit and obtained higher reliability compared to the seven-item version (0.82).[3] In the study of the instrument's Canadian version,[14] the reliability analysis of the scale applied to 1,377 older adults showed an alpha of 0.51 to 0.54 for the seven-item version, rising to 0.72 to 0.76 in the analysis of the five-item version. The same is true of the psychometric analysis of the Japanese version of the scale, conducted with 2,067 residents aged between 25 and 74 years, which showed better internal consistency for the version without inversely scored items, from 0.69 to 0.77.[12]

Although the difference in reliability between the seven-item and five-item scales was not as pronounced in the present sample, further investigation of the reduced version (five items) confirmed that this version provides a better fit to the model than the seven-item scale, as observed in previous studies.[3,12–14] When reviewing the instrument's structure, one possible reason for the poor performance observed in the withdrawn items could be the effects of their inverted wording, which makes it difficult to measure the construct they were intended to measure.[3,11] The study of translation and cultural adaptation of the instrument to its Brazilian version considered all items of the original scale. Through factor analysis, this study showed that the removal of items with inverted scores demonstrated greater reliability and a better model fit. Future studies could consider changing the wording of positively worded items to understand whether their performance is related to qualitative aspects or is purely an effect of the method.

Correlation analysis between sense of mastery and perceived burden, depressive symptoms, anxiety, and quality of life indicated that the PMS-BR-reduced version has validity based on relationships with related constructs. Given that sense of mastery is an important psychological mechanism that mediates burden and is an important protector of mental well-being,[3,12] these results indicate that the PMS-BR has criterion validity. Therefore, having a high level of mastery is important for caregivers of people living with dementia, as this context implies vulnerability to anxiety and depression, influencing their burden perception.[4,12,34,35]

The negative correlation between the sense of mastery and the negative impacts of caring can be attributed to the psychological protection provided by higher mastery levels compared to those with lower mastery levels, which also results in less manifestation of psychological symptoms such as depression and anxiety.[3] Similarly, the positive correlation between the sense of mastery and the caregivers' quality of life reinforces the protective role of this coping mechanism. Other studies corroborate this finding and point to a relationship between mastery and other positive care aspects, such as positive self-perception of health, self-efficacy, and life satisfaction, suggesting a sense of mastery as a mediating phenomenon between perceived burden and psychological symptoms.[3,12,36,37]

A limitation of this study concerns the selection of participants, which was restricted by inclusion criteria based on specific scores on certain measures. Additionally, since this study is part of a larger project, the sample may have been further limited and might not fully represent the diverse experiences of caregivers of people with

dementia in Brazil. Another relevant limitation is the linguistic nuances of Brazilian Portuguese spoken in different regions of Brazil. The PMS-BR version may have difficulty in capturing linguistic and cultural variations in mastery perceptions among caregivers, especially considering the vast cultural and regional contexts of Brazil. The different forms of expression and interpretation of terms related to mastery and burden may have influenced the responses in a non-uniform manner. Therefore, future research should consider the regional particularities of Brazilian Portuguese, addressing both the translation and cultural validation of assessment instruments.

CONCLUSION

The assessment of the sense of mastery through the PMS-BR in unpaid caregivers of people living with dementia in Brazil provides a valuable contribution to the theoretical understanding of this construct in caregiving contexts. The construct validation and reliability of the PMS-BR were successful, demonstrating its high reliability for evaluating the effectiveness of interventions aimed at supporting caregivers.

These findings reinforce the relevance of mastery as a psychological coping mechanism, mitigating the effects of caregiver burden and psychological symptoms. Future research should continue to explore and strengthen the theoretical framework surrounding the sense of mastery in this population, with additional studies validating the instrument and examining its potential impact on caregiving strategies and outcomes.

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Premenstrual Syndrome-Impact Questionnaire: Cross-cultural adaptation, reliability, and validity of the Turkish version

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ABSTRACT

BACKGROUND: Short and practical questionnaires and tests that assess premenstrual symptoms and premenstrual syndrome (PMS) are required.

OBJECTIVES: This study aimed to investigate the cross-cultural adaptation, validity, and reliability of the Premenstrual Syndrome Impact Questionnaire (PMS-IQ) in Turkish women with PMS.

DESIGN AND SETTING: The reliability and validity of the questionnaire were evaluated in Tokat, Türkiye.

METHODS: A convenience sample of 146 individuals diagnosed with PMS was used to assess the reliability and validity of the Turkish version of the PMS-IQ. Test-retest analyses were performed in a subset of 96 individuals one week after the initial assessment. Construct validity was evaluated through convergent validity analysis using the Premenstrual Syndrome Scale (PMSS) and the Premenstrual Symptoms Impact Survey (PMSIS), and divergent validity analysis with the Big Five Inventory-10 (BFI-10).

RESULTS: Cronbach's α values for the total score and subscales ranged from 0.861 to 0.917, whereas the test-retest reliability values ranged from 0.755 to 0.847. Factor analysis indicated that the scale had a three-factor structure. The total PMS-IQ score was significantly correlated with both the PMSS ($r = 0.718$) and PMSIS ($r = 0.774$), but showed no significant correlation with the BFI-10 ($r = 0.113$). No floor or ceiling effects were observed for the total or subscale scores of the PMS-IQ.

CONCLUSIONS: The Turkish version of the PMS-IQ demonstrated reliability and validity for evaluating individuals with PMS.

CLINICAL TRIAL REGISTRATION: This study is registered at ClinicalTrials.gov (identifier: NCT05725447).

INTRODUCTION

Menstruation is a physiological process that recurs monthly for approximately 30–35 years, significantly affecting women's lives.[1] Women in Turkey commonly experience premenstrual syndrome (PMS).[2,3] PMS is characterized by a cluster of physical, behavioral, and emotional symptoms that manifest during the luteal phase and subside with the onset of menstruation or shortly thereafter.[4] Although the exact causes of PMS remain unclear, it is believed to be associated with hormonal changes, neurotransmitters, prostaglandins, dietary habits, medications use, and lifestyle factors.[5] Approximately 90% of women of reproductive age group report experiencing premenstrual symptoms of varying severity.[4] Emotional and mood-related symptoms frequently observed in PMS include mood swings, depression, anger, irritability, changes in sadness, tension, heightened sensitivity, and crying. Physical symptoms may include weight gain, abdominal cramps, acne, fatigue, breast tenderness, and bloating.[6]

Considering individual and psychological differences, it is important to manage mild to severe PMS symptoms during each menstrual cycle. Occasionally, the symptoms become severe enough to adversely influence daily activities. PMS is also associated with significant psychological issues.[7,8] Studies conducted among students have shown that those experiencing moderate to severe PMS symptoms report difficulties in concentration, acute psychological distress, decreased academic achievement, and negative thoughts.[9,10] Various interventions, including relaxation techniques, have been investigated for the management of PMS.[11] If left untreated, severe PMS symptoms may worsen mental status in response to personal and environmental stressors, potentially leading to the development of premenstrual dysphoric disorder (PMDD), a more severe form of PMS.[12,13]

Most PMS questionnaires measure the presence and/or severity of past and future symptoms rather than the impact of those symptoms.[14–16] The Premenstrual Syndrome Impact Questionnaire

(PMS-IQ), comprising 18 items, is designed to evaluate functional interactions and psychological stress associated with premenstrual symptoms in daily life. The PMS-IQ evaluates the impact of the complex and multifaceted nature of PMS, facilitates the diagnostic process, and enables the planning and evaluation of treatment.[17]

OBJECTIVES

Questionnaires and tests that assess premenstrual symptoms and PMS are required. Broadening the range of assessment approaches would enable more comprehensive evaluation of the disorder. This cross-cultural adaptation study aimed to validate a self-administered Turkish version of the PMS-IQ (PMSIQ/T).

METHODS

Individuals

The study sample comprised women aged 18–45 years with PMS, including students and employees of Tokat Gaziosmanpaşa University. All participants were informed of the study's aim and methodology, which were approved by the Ethics Committee of Tokat Gaziosmanpaşa University (decision date: November 3, 2022; decision no: 83116987-760). Eligibility required meeting the provisional diagnostic criteria for PMDD as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th Edition,[18] confirmed through a prospective screening process.

The exclusion criteria were as follows: (1) presence of bipolar disorder, psychosis, moderate to severe depression, eating disorder, or somatic symptom disorders; (2) current or previous participation in a physiotherapy program due to PMS symptoms; (3) immediate suicidal inclinations; (4) pregnancy, childbirth, or breastfeeding within the last 3 months; (5) gynecological conditions such as infertility, hysterectomy, endometriosis, oophorectomy, polycystic ovarian syndrome, or gynecological cancer; and (6) initiation or changes in the use of contraceptive tablets, antidepressants, hormones (e.g., thyroid hormones), or benzodiazepines/antipsychotics within the last 3 months.

The required sample size was calculated as 99, based on an expected intraclass correlation coefficient (ICC) of $\rho 1 = 0.85$,[19] a minimal acceptable reliability level of $\rho 0 = 0.75$,[13] with $\alpha = 0.05$ and $\beta = 0.20$.

A total of 192 women were initially recruited. Forty-six were excluded due to either gynecological diseases (n = 15) or failure to meet PMDD criteria (n = 31). Thus, the final sample included 146 participants (**Figure 1**). Before the study began, all participants were informed about the study, voluntarily agreed to participate in accordance with the principles of the Helsinki Declaration, and formally signed an informed consent form.

Procedure

Before commencing the study, approval was obtained from J. N. Kues,[17] the developer of the PMS-IQ. The language translation and cultural adaptation process of the PMS-IQ followed the methodology outlined by Beaton.[20] The original questionnaire was independently translated into Turkish by two individuals (a physiotherapist who was unaware of the study and an English linguist). These translators than collaborated to merge their translations into a single version. Subsequently, two certified translators independently performed a back-translation of the merged

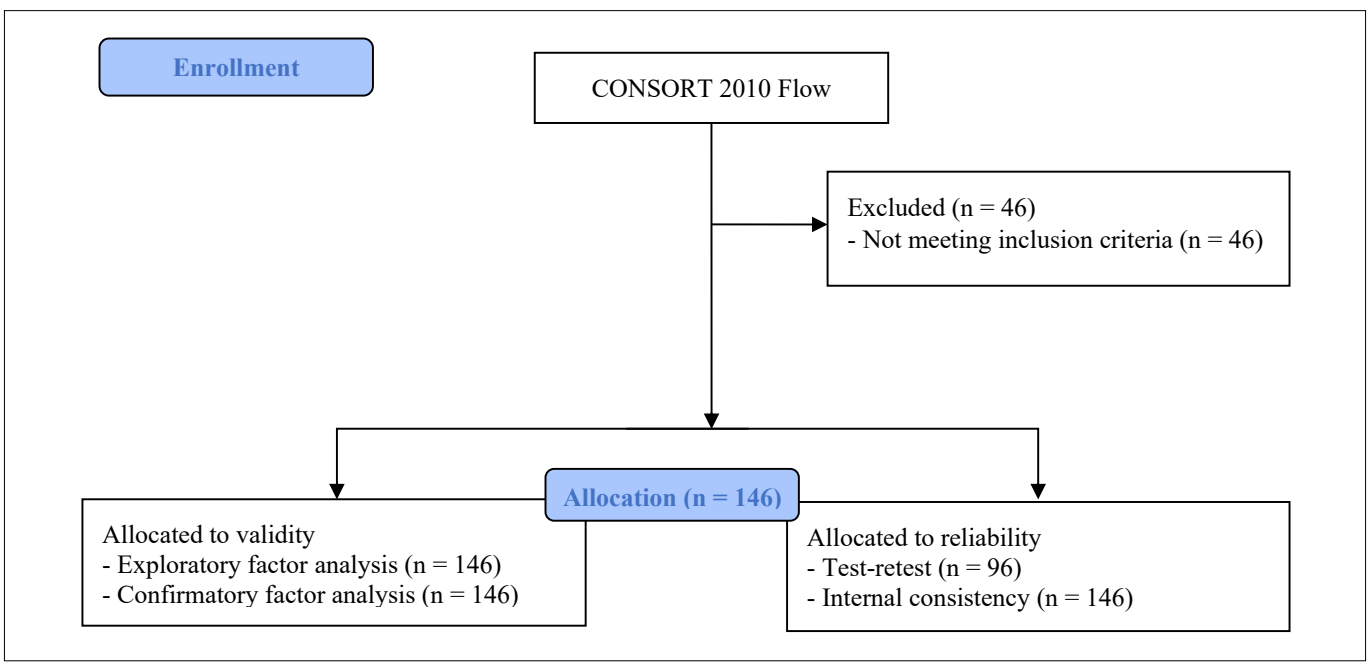

Figure 1. Flowchart of participant recruitment.

Turkish version into English. The version translated back into English from Turkish was reviewed by a translation team (a physiotherapist, an English linguist, and two certified translators), who evaluated its compatibility with the original questionnaire. A clarity form was developed for each question in the questionnaire and piloted. During the pretest phase, 146 individuals with PMS were assessed for their comprehension of the items and wording, as well as their ability to complete the questionnaire.[20] Comprehensibility of the questionnaire was evaluated using a binary scoring system, with responses recorded as either "yes" or "no". If a participant responded "no" for comprehensibility, they were asked to identify the unclear items and explain the reason. Based on the results of the pretest phase, no modifications were made to the pre-final version of the PMS-IQ/T.

Measures

Premenstrual Syndrome Scale (PMSS): The PMSS was developed by Gençdoğan in 2006 to access the severity of premenstrual symptoms based on DSM-III and DSM-IV-R criteria. Widely used in Turkey, the scale consist of 44 items, each referring to experiences "one week before menstruation". It covers nine dimensions: depressive affect, anxiety, fatigue, irritability, depressive thoughts, pain, appetite changes, sleep changes, and bloating. Each item is rated on a five-point Likert scale ranging from 1 to 5. The PMSS total score ranges from 44 to 220 points. Dimensional scores are calculated by summing the items within each dimension, and the overall PMSS score is derived by summing the scores of each dimension. Individuals with a total score exceeding 50% are categorized as PMS-positive. A high PMSS score is indicative of intense premenstrual symptoms.[21]

Premenstrual Symptoms Impact Survey (PMSIS): Wallenstein et al. developed the PMSIS, a six-item scale designed to assess the influence of premenstrual symptoms on health-related quality of life. The scale consists of six items that assess the impact of premenstrual symptoms on various aspects of quality of life, including cognitive well-being, interpersonal interaction, liveliness, and responsibility management. Each is rated on a five-point scale, from 1 (no impact) to 5 (high impact), reflecting the severity of the impact on various aspects of quality of life. Total scores range from 6 to 30, with higher scores indicating a decrease in the quality of life associated with the impact of premenstrual symptoms.[16] Güler et al. conducted a validity and reliability study of the Turkish version of the PMSIS. The scale is proficient in evaluating the condition and treatment outcomes of PMS in women of reproductive age.[22]

Big Five Inventory-10 (BFI-10): The BFI-10 was introduced by Rammstedt and John as a concise alternative to the longer BFI-44.[23] The scale comprises 10 items organized into five sub-dimensions. Responses are rated on a 5-point response scale: "disagree strongly," "disagree a little," "neither agree nor disagree," "agree a little," and "agree strongly." Statements 1, 3, 4, 5, and 7 are inverted on the scale. The Turkish version of the BFI-10 has been validated and shown to be reliable.[24]

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and LISREL version 8.80 (Scientific Software International, Inc., Lincolnwood, IL, USA). Data are presented as mean ± standard deviation, median (minimum–maximum), and percentage (%). The Kolmogorov–Smirnov test was used to determine whether the numerical variables were normally distributed.

Internal consistency and test-retest reliability analyses were conducted to assess the reliability of the PMS-IQ. Cronbach's α was employed for internal consistency analysis, whereas the ICC with a 95% confidence interval was used for the test-retest analysis. A Cronbach's α value ≥ 0.80 is considered an acceptable threshold,[25] whereas an ICC score ≥ 0.75 is considered acceptable for test-retest reliability.[26]

Reproducibility was examined using the minimum detectable change (MDC) and the standard error measurement (SEM). The following formulae were applied:[27]

- MDC_{95}: $z \times SEM \times \sqrt{2}$, where z = 1.96 (based on 95% confidence) and SEM is the standard error of the measurement;
- SEM_{95}: $SD \times \sqrt{1 - ICC}$, where SD is the standard deviation of the participants, and ICC is the reliability coefficient.

Exploratory factor analysis (EFA) was conducted to assess the structural validity of the PMS-IQ. Before factor analysis, sample suitability was evaluated using Bartlett's test, and sample adequacy was assessed using the Kaiser–Meyer Olkin test.[28] Confirmatory factor analysis (CFA) was performed to validate and confirm the factor structure identified in the initial analysis. The fit indices supporting this analysis were also examined.[29]

Convergent and divergent validity were assessed for construct validity using Pearson's and Spearman's correlation analyses. The convergent and divergent validity of the PMS-IQ/T was determined based on the total and subscale scores obtained from the PMS-IQ, PMSS, PMSIS, and BFI-10. Correlation coefficients were interpreted according to established thresholds in medical research: 0.90-1.00 (very high), 0.70-0.90 (high), 0.50-0.70 (moderate), 0.30-0.50 (low), and 0.00-0.30 (negligible).[30]

The percentages of the lowest and highest values for the PMS-IQ/T and its subscales were calculated to assess ceiling and floor effects.[31] $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 outlines the characteristics of the participants. A total of 146 Turkish-speaking females with PMS completed the questionnaire, of whom 96 completed it at the second time point.

Internal consistency, as measured by Cronbach's α, was excellent (α = 0.917). Test–retest reliability of the PMS-IQ/T was also very high (ICC = 0.847; 95% CI = 0.780-0.895). The SEM for the total score was 3.79, and the MDC was 10.50. Cronbach's α, ICC, SEM, and MDC values for the total and subscale scores are presented in **Table 2**.

The mean scores of the PMS-IQ/T, corrected item-total correlations, and Cronbach's α for item deletion are presented in **Table 3**.

Table 1. Numerical and categorical characteristics of participants in the test and retest groups

Numeric variables	Mean (SD) (test) (n = 146)	Mean (SD) (retest) (n = 96)
Age (years)	20.69 (1.96)	20.94 (2.18)
Menarche age (years)	13.15 (1.31)	13.28 (1.29)
Weight (kg)	58.06 (9.86)	57.68 (10.32)
Height (cm)	163.64 (6.10)	163.72 (6.04)
BMI (kg/m^2)	21.73 (3.33)	21.61 (3.58)
Categorical variables	n (%)	n (%)
Menstrual cycle		
20 days and less	8 (5.5 %)	4 (4.2 %)
21-33 days	122 (83.6 %)	82 (85.4 %)
34 days and more	16 (10.9 %)	10 (10.4 %)
Menstrual order		
Yes	115 (78.8 %)	72 (76.6 %)
No	31 (21.2 %)	22 (23.4 %)
Premenstrual drug use		
Yes	45 (30.8 %)	31 (32.3 %)
No	101 (69.2 %)	65 (67.7 %)
Menstrual drug use		
Yes	55 (37.7 %)	40 (41.7 %)
No	37 (25.3 %)	21 (21.9 %)
Sometimes	54 (37.0 %)	35 (36.4 %)
Smoking		
Yes	23 (15.8 %)	14 (14.6 %)
No	123 (84.2 %)	82 (85.4 %)
Use of alcohol		
Yes	5 (3.4 %)	5 (5.2 %)
No	141 (96.6 %)	91 (94.8 %)
Painful menstruation		
No	4 (2.7 %)	3 (3.1 %)
Mild	18 (12.3 %)	11 (11.5 %)
Moderate	41 (28.1 %)	24 (25.0 %)
Severe	63 (43.2 %)	44 (45.8 %)
Seriously	20 (13.7 %)	14 (14. 6%)

SD = standard deviation; BMI = body mass index.

The Kaiser–Meyer–Olkin (KMO) test confirmed the adequacy of the sample for analysis (KMO = 0.884). The correlations between the items of the PMS-IQ/T were deemed sufficient for analysis, as evidenced by Bartlett's sphericity test (chi-squared = 1219.442, P < 0.001). After removing factors with eigenvalues > 1, the 18 items of the PMS-IQ/T were associated with three factors. **Figure 2** shows the distribution of the eigenvalues through a scree plot. This factor structure explained 55.996% of the total variance, which is considered satisfactory as it accounts for > 50% of the total variance in the PMS-IQ/T. According to the EFA results, all factor loadings were above 0.40 (**Table 4**).

The three factors observed in the EFA were confirmed using CFA. The comparative Fit Index, Tucker-Lewis Index, Incremental Fit Index, Chi-square/Degrees of freedom, Consistent Akaike Information Criterion, Expected Cross-Validation Index, and Root Mean Square Error of Approximation were 0.95, 0.95, 0.95, 2.11, 511.36, 2.46, and 0.087, respectively, according to the CFA results. These values are considered excellent and acceptable.[29]

Table 3. Mean scores, corrected item-total correlations, and Cronbach's α if item deleted for the Turkish version of the Premenstrual Syndrome Impact Questionnaire (n = 146)

Item	Mean	SD	Corrected item-total correlation	Cronbach's α if item deleted
1	2.47	0.78	0.567	0.913
2	2.76	0.79	0.489	0.914
3	2.66	0.89	0.501	0.914
4	1.57	0.70	0.456	0.915
5	2.34	0.88	0.505	0.914
6	1.75	0.98	0.324	0.919
7	1.83	0.88	0.648	0.910
8	2.10	1.03	0.677	0.909
9	2.30	0.87	0.671	0.910
10	1.75	0.85	0.614	0.911
11	2.43	0.95	0.551	0.913
12	2.01	0.95	0.531	0.913
13	2.50	0.99	0.736	0.908
14	2.62	0.96	0.627	0.911
15	2.33	0.96	0.684	0.909
16	2.14	0.94	0.675	0.910
17	2.39	0.93	0.590	0.912
18	2.39	1.03	0.735	0.908

SD = standard deviation.

Table 2. Test–retest reliability and internal consistency of the Turkish version of the Premenstrual Syndrome Impact Questionnaire (n = 96)

	Baseline Mean ± SD	Retest Mean ± SD	P	Test – retest (ICC and 95% CI)	SEM	MDC	Internal consistency (Cronbach's α)
PMS-IQ/T total score	40.54 ± 9.84	40.46 ± 9.54	0.879	0.847 (0.780-0.895)	3.79	10.50	0.917
Factor 1	19.65 ± 6.15	19.68 ± 5.91	0.932	0.824 (0.747-0.879)	2.53	7.02	0.903
Factor 2	9.02 ± 2.53	9.13 ± 2.49	0.561	0.758 (0.657-0.831)	1.24	3.43	0.862
Factor 3	11.76 ± 2.45	11.45 ± 2.32	0.070	0.755 (0.654-0.830)	1.18	3.27	0.861

PMS-IQ/T = Turkish version of the Premenstrual Syndrome Impact Questionnaire; SD = standard deviation; ICC = intraclass correlation coefficient; CI = confidence intervals; SEM = standard error measurement; MDC = minimal detectable change.

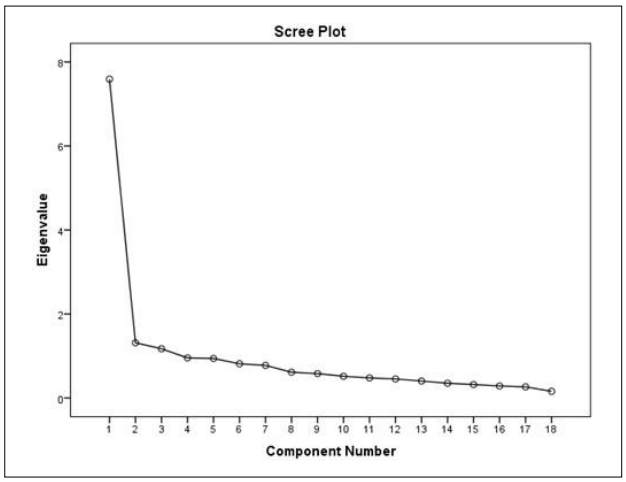

Figure 2. Scree plot of the Turkish Version of the Premenstrual Syndrome Impact Questionnaire (n = 146).

Table 4. Factor analysis results for the Turkish version of the Premenstrual Syndrome Impact Questionnaire (n = 146)

Item	Factor 1	Factor 2	Factor 3
7	0.653		
8	0.711		
10	0.704		
11	0.588		
12	0.637		
13	0.641		
15	0.695		
16	0.669		
18	0.691		
6		0.436	
9		0.515	
14		0.795	
17		0.752	
1			0.570
2			0.564
3			0.715
4			0.545
5			0.695
Percent variance (%)	42.176	49.480	55.996

Kaiser-Meyer-Olkin Measure of Sampling Adequacy = 0.884; Bartlett's Test of Sphericity = 1219.442; Total variance = 55.996%.

Convergent validity analysis revealed that the PMS-IQ/T was significantly correlated with the PMSS and PMSIS (**Table 5**). Divergent validity results indicated a non-significant correlation with the BFI-10. Recognizing the established association between neuroticism and premenstrual symptoms related to anxiety,[32] the original study predicted a low but noteworthy correlation with the neuroticism scale.[17]

The floor effect percentages were 0.7%, 2.7%, 5.5%, and 0.7% for the total score and factors 1, 2, and 3, respectively. The ceiling effects percentages were 0%, 0.7%, 1.4%, and 0.7%, respectively. No ceiling or floor effects were observed in the PMS-IQ/T or its subscales, as all values were < 15%.

DISCUSSION

This study investigated the validity and reliability of the PMS-IQ/T in Turkish women diagnosed with PMS. The PMS-IQ/T demonstrated superior reliability and strong validity in evaluating functional interference and psychological distress.

Many instruments and screening tools have been developed to evaluate PMS. These include the Daily Record of Severity of Problems, Premenstrual Screening Tool (PSST), Premenstrual Record of Impact and Severity of Menstruation, Calendar of Premenstrual Experiences, Daily Symptom Report,[33] Premenstrual Assessment Form (PAF),[34] Premenstrual Coping Measure (PCM),[35] PMSS,[21] and PMSIS.[16] The validity and reliability of the PSST,[18] PAF,[36] PCM,[37] PMSS,[21] and PMSIS[22] have been examined in Turkish population. The Cronbach's α coefficient of the Turkish version of the PSST was 0.92.[18] The internal consistency of the PAF yielded a Cronbach's α of 0.97.[36] For the PCM subscores, Cronbach's α values ranged from 0.751 to 0.890, and ICC ranged from 0.712 to 0.734.[37] The PMSS had a Cronbach's α of 0.75 and an ICC of 0.87.[21] The PMSIS showed a Cronbach's α of 0.89.[22] In the original version of the PMS-IQ, the subscales had a Cronbach's α of 0.90.[17] In the present study, the PMS-IQ/T demonstrated Cronbach's α values ranging from 0.861-0.917 and ICCs from 0.755-0.847 for the total score and subscales. These findings are consistent with previous literature and confirm the excellent reliability of the PMS-IQ/T. The Bland-Altman plots further supported these results.

The SEM is a reliability measure that evaluates the stability of responses across multiple measurements. It represents amount of error attributable to measurement variability. The MDC refers to the smallest perceptible and significant change in an evaluated parameter, indicating a change not due to measurement error. Both measurements are considered indicators of reliability.[26] The SEM value was 3.79 points, corresponding to 9.36% of the mean PMS-IQ/T score and 5.26% of the maximum score. The MDC value, calculated based on the SEM, was 10.50 points, which equates to 25.93% of the average value. Given the maximum score of 72 points, 10.50 points represents 14.58% of the maximum value.

When the corrected item-total correlation values of the PMS-IQ/T were examined, moderate to high correlations were observed, indicating generally high correlations. The Cronbach's α values for item deletion supported the inclusion of all 18 items in the PMS-IQ/T. Removing any item did not result in a Cronbach's α value higher than that of the total score (0.917), except for one item. For item 6, this value (0.919) was very close to the overall Cronbach's α. Therefore, all items were included in the PMS-IQ/T.

The original version of the PMS-IQ exhibited a two-factor structure, as confirmed by both EFA and CFA. Following EFA,

Table 5. Correlations between the Turkish version of the Premenstrual Syndrome Impact Questionnaire and its subscales with other questionnaires for convergent and divergent validity (n = 146)

	PMS-IQ total	Factor 1 (psychological impact)	Factor 2 (recreational and emotional impact)	Factor 3 (motivational impact)
Convergent validity				
PMSS	**0.718**** μ	**0.712****	**0.480**** μ	**0.593**** μ
-Depressive feelings	**0.597**** μ	**0.634****	**0.316**** μ	**0.529*** μ
-Anxiety	**0.568****	**0.612****	**0.338****	**0.397****
-Fatigue	**0.569****	**0.530****	**0.450****	**0.529****
-Irritability	**0.571****	**0.552****	**0.365****	**0.512****
-Depressive thinking	**0.701**** μ	**0.695****	**0.483**** μ	**0.539**** μ
-Pain	**0.524****	**0.491****	**0.452****	**0.370****
-Changed appetite	0.108	0.138	0.022	0.096
-Changed sleep	**0.458****	**0.433****	**0.329****	**0.393****
-Swelling	**0.293****	**0.300****	**0.223****	**0.246****
PMSIS	**0.774****	**0.741****	**0.591****	**0.586****
Discriminant validity				
BFI-10	0.113 μ	0.130	0.129 μ	0.089 μ
-Extraversion	-0.140 μ	-0.139	-0.083 μ	-0.079 μ
-Agreeableness	-0.063 μ	-0.121	0.013 μ	-0.032 μ
-Conscientiousness	0.042 μ	0.073	-0.029 μ	-0.025 μ
-Neuroticism	**0.300**** μ	**0.284****	**0.165*** μ	**0.294**** μ
-Openness	**0.199*** μ	**0.195***	**0.251**** μ	0.103 μ

PMS-IQ = Premenstrual Syndrome Impact Questionnaire; PMSS = Premenstrual Syndrome Scale; PMSIS = Premenstrual Symptoms Impact Survey; BFI-10 = Big Five Inventory-10.
μ Pearson correlation analysis.

the total variance was 52.11%. The sub-dimensions were named "psychological impact" and "functional impact".[17] Both the EFA and scree plot for the PMS-IQ/T revealed a three-factor structure, with each factor having an eigenvalue greater than one. The variance percentage for three factors obtained through the EFA was 55.996%, which is considered acceptable. As a result, PMS-IQ/T was segmented into three distinct subscales: "psychological impact," "recreational and emotional impact," and "motivational impact."

Divergent and convergent validity of the original PMS-IQ were assessed using the BFI-10 and PDI, with results indicating notable positive correlations ranging from low to high.[17] The PMS-IQ/T demonstrated both convergent and divergent validity, supported by significant correlations between the PMS-IQ/T and its subscales with the PMSS, PMSIS, and BFI-10. A strong positive correlation was observed between the PMS-IQ/T and both the PMSS and PMSIS, whereas a weaker correlation was found with the BFI-10. The divergent validity results using the BFI-10 were consistent with those of the original study. Moderate and high correlations between the PMS-IQ/T and the total scores and subscales of the PMSS and PMSIS indicated good validity.

While extensive statistical analyses were conducted to evaluate the psychometric properties of the PMS-IQ/T, a limitation of this study is the absence of responsiveness assessment. Consequently, further studies are warranted to assess responsiveness by determining the minimum clinically important differences. Further studies should also examine the diagnostic accuracy of the PMS-IQ/T in predicting PMS. In addition, the sensitivity and specificity of the PMS-IQ/T should be investigated.

CONCLUSION

Based on the outcomes of this study, the PMS-IQ/T emerged as a robust and internally consistent tool, demonstrating validity and reliability in the assessment of individuals with PMS. These findings suggest that the PMS-IQ/T is suitable for use in both clinical practice and research settings.

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Effects of unsupervised walking on walk performance and functional mobility in individuals with chronic stroke: a blind randomized clinical trial

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ABSTRACT

BACKGROUND: What are the effects of walking training on the ground in an unsupervised manner and with different weekly durations after chronic stroke?

OBJECTIVE: To compare the effects of unsupervised walking for 150 and 300 minutes per week on walking performance, speed, and functional mobility in individuals with chronic stroke.

DESIGN AND SETTING: Randomized clinical trial was conducted at Rede Sarah Rehabilitation Hospital (São Luís, Brazil).

METHODS: Individuals included (n = 40) were assessed using the 6-minute walk test (6MWT), functional mobility using the Timed Up and Go (TUG) test, and the Five Times Sit to Stand Test (FTSST). They were assigned to the two experimental groups and instructed to walk 150 (G150) or 300 minutes per week (G300) and to perform unsupervised gait training for the next eight weeks.

RESULTS: No significant differences were observed between the group factors and no significant interaction was found for the group × time interaction, indicating that G150 and G300 changed similarly. The comfortable walking speed increased for both G150 and G300, resulting in a large effect size. Performance on the TUG and 6MWT also improved, but the effect size was small. For maximum walking speed, despite the improvement in performance in G150 and the G300, effect size was medium for both groups. The same was true for the FTSST.

CONCLUSION: Unsupervised walking was effective in improving gait performance and functional mobility in individuals with chronic stroke regardless of the recommended weekly duration (150 or 300 minutes).

CLINICAL TRIAL REGISTRATION: RBR-5g4g9bq (https://ensaiosclinicos.gov.br/rg/RBR-5g4g9bq).

INTRODUCTION

Studies have evaluated the contribution of gait training to safe and independent walking in individuals with chronic stroke, showing improvements in comfortable and maximal walking speed (determined from the 10-meter walk test),[1–5] walking endurance as measured by the distance covered in the 6-minute walk test (6MWT),[1–6] and functional mobility as measured by the time spent performing the Timed Up and Go (TUG) test.[7,8] Less commonly, the task of standing up from a seated position has also been used to measure functional mobility after exercise programs, with assessment using the Five Times Sit to Stand Test (FTSST).[9]

Regarding exercise volume, which is also prescribed as a weekly duration, guidelines for adults after stroke suggest positive outcomes, even with protocols that vary in weekly duration. For example, the American Stroke Association, one of the main guidelines for stroke, recommends a weekly duration of 150 to 300 minutes of light-to-moderate intensity exercise.[10,11] Although there is evidence that exercise volume positively correlates with walking performance after stroke,[7] studies using walking as an intervention used volumes close to or equal to 150 minutes per week; a minimum amount is also recommended to reduce sedentary lifestyle and its complications.[5,12,13]

However, although the weekly duration of 150 minutes has been shown to be effective in these studies, the training programs were conducted with specific walking equipment (treadmills) and/or with close professional supervision, factors that make it difficult for people to implement and

maintain the exercises of individuals who have already completed rehabilitation programs.[11] Unsupervised walking without the use of equipment is expected to allow for greater patient engagement, but with the disadvantage that the exercise load performed may be less than planned because of the lack of direct monitoring.[7,10]

We hypothesized that unsupervised walking would be as effective as supervised walking in individuals with chronic stroke. Therefore, we compared the effects of unsupervised walking for 150 or 300 minutes per week on walking performance (6MWT),[6] speed, and functional mobility (TUG[14,15] and FTSST[9]) of individuals with chronic stroke.

METHODS

Trial design and ethical aspects

Randomized clinical trial was according to CONSORT.[16] Participants were evaluated at three time points: clinical enrolment, pre-intervention, and post-intervention. This study was approved by the Brazilian Registry of Clinical Trials (report number: RBR-5g4g9bq) and the Research Ethics Committee (report number: 3739370). Data collection for the current study was performed during routine care at the Rede Sarah de Hospitais, São Luís, Brazil, from May 20, 2019, to December 31, 2020.

Individuals were evaluated at regular follow-up visits and in the hospital on three different days: on admission, before the intervention (pre), and at the end of the intervention (post). On admission, after the assessment of cardiovascular risk factors under the guidance of a clinical physician, an exercise specialist (the investigator of this study) performed tests to assess comfortable and maximal walking speed using the 10-meter sprint test,[6] walking endurance using the 6MWT,[6] and functional mobility using the TUG test[14,15] and FTSST.[9]

After the initial assessments, individuals were advised to return home, maintain their usual routine, and return to the hospital after eight weeks (review care). This eight-week interval was used to carry out the randomization of the sample, to allow for the availability of places for team care, and for the logistical organization of the use of institutional space. No interventions were administered during this period.

After the first eight weeks (period of no intervention since admission), individuals returned for review, re-evaluation, and instruction (pre). On this day, they were instructed to perform unsupervised gait training for the next eight weeks according to the instructions provided, knowing only the gait protocol they were to perform. The unsupervised walking training period was identical for both experimental groups. At the end of these eight weeks of unsupervised walking training, individuals returned for a new review for reassessment and final instruction (post).

Participants

Individuals included were in the normal course of care at the hospital; that is, they had already undergone some form of follow-up with the rehabilitation team at some point after stroke. Inclusion criteria for the sample were as follows: diagnosis of a stroke that occurred at least 6 months ago, supported by a medical report; and comfortable walking speed (CWS) of less than 1.0 m/s, i.e., limited (0.4 m/s to 0.8 m/s) and unrestricted (0.8 m/s to 1.0 m/s) community ambulators.[10,11]

Speed was measured on the day of admission by walking time in the 10-meter test;[6] having participated in a motor rehabilitation program at any time after the stroke; and not having participated in any physical training or rehabilitation programs during the study period or in the previous six months. The following conditions were considered as sample exclusion criteria: any clinical condition that made it impossible to perform examinations and assessments; inability to walk at least 10 meters without assistance;[6] and cognitive deficits that made it difficult to understand simple verbal commands, as identified by previous medical records using the Mini-Mental State Examination with a score below 23 points.[10,11]

The individuals who were unable to complete at least 80% of their planned weekly volumes during the training period were excluded. This methodological criterion was adopted to increase the possibility of expected changes in performance depending on the totality of the oriented durations. Furthermore, individuals excluded by the exclusion criteria would participate without distinction in all care throughout the follow-up period so that their rehabilitation program would be identical to that of the others.[10,11]

Randomization

Stratified randomization was performed by a third party blinded to the research content and was used to reduce group heterogeneity due to differences in walking speed, despite the fact that all individuals met the inclusion criteria.[17] For this process, individuals were listed and classified according to their CWS (measured by the 10-meter test on the day of admission) as limited community ambulators (speed between 0.4 m/s and 0.8 m/s) or unlimited (speed greater than 0.8 m/s).

Half of the individuals in each classification were then randomly assigned to two experimental groups and instructed to walk for 150 minutes (G150) or 300 minutes (G300) per week. Thus, with stratified randomization, both groups had similar proportions of limited and unlimited community ambulation (**Figure 1**).

Interventions

The unsupervised walking training lasted for eight weeks and was conducted in the community. Individuals were instructed on the correct use of medications, best time and place to walk (avoiding uneven terrain, excessive sun exposure, and high temperatures),

and the need for adequate hydration and nutrition. Safety and fall prevention should be prioritized using mobility devices (if used).

Each group was instructed to perform one of the two proposed weekly durations of unsupervised walking (150 or 300 minutes). The existence of a second protocol was not disclosed; that is, each group knew only the exercise program they were to perform. The G150 group was asked to walk for 30 minutes per day (five days per week), a methodological criterion adopted to equalize the frequency of training between the groups, thus allowing a regular distribution of the prescribed durations throughout the week. They were instructed to maintain the highest sustainable walking speed as exercise intensity, an effective parameter to promote functional recovery in individuals with chronic stroke.[18] The G300 group was instructed to walk 60 minutes per day (five days per week).

To determine the effort exerted, individuals were asked to record the Borg Rating of Perceived Exertion (RPE) scale during each training session in a diary prepared and provided by the team on the second day of the assessment (pre).[19,20] The RPE scale[19,20] was presented to them in detail on that day, with the score reinforced based on the verbal anchors of the instrument, emphasizing and exemplifying the initial anchor (no effort) and final anchor (maximum effort already made). The use of diaries is common for monitoring training performed outside of rehabilitation centers.[21] This diary included all possible exercise days during the eight-week period and was accompanied by a RPE.[19,20] Individuals were asked to complete it by answering three items: "Put an 'X' on the day you exercised"; "How many minutes did you walk?"; "Perceived exertion (rate from 6 to 20)." The intensities were considered light (RPE < 11), moderate (RPE 11–14), or high (RPE > 14).

Another methodological criterion adopted in accordance with the guidelines was the possibility of delivering training continuously or at regular intervals. Since the individuals had

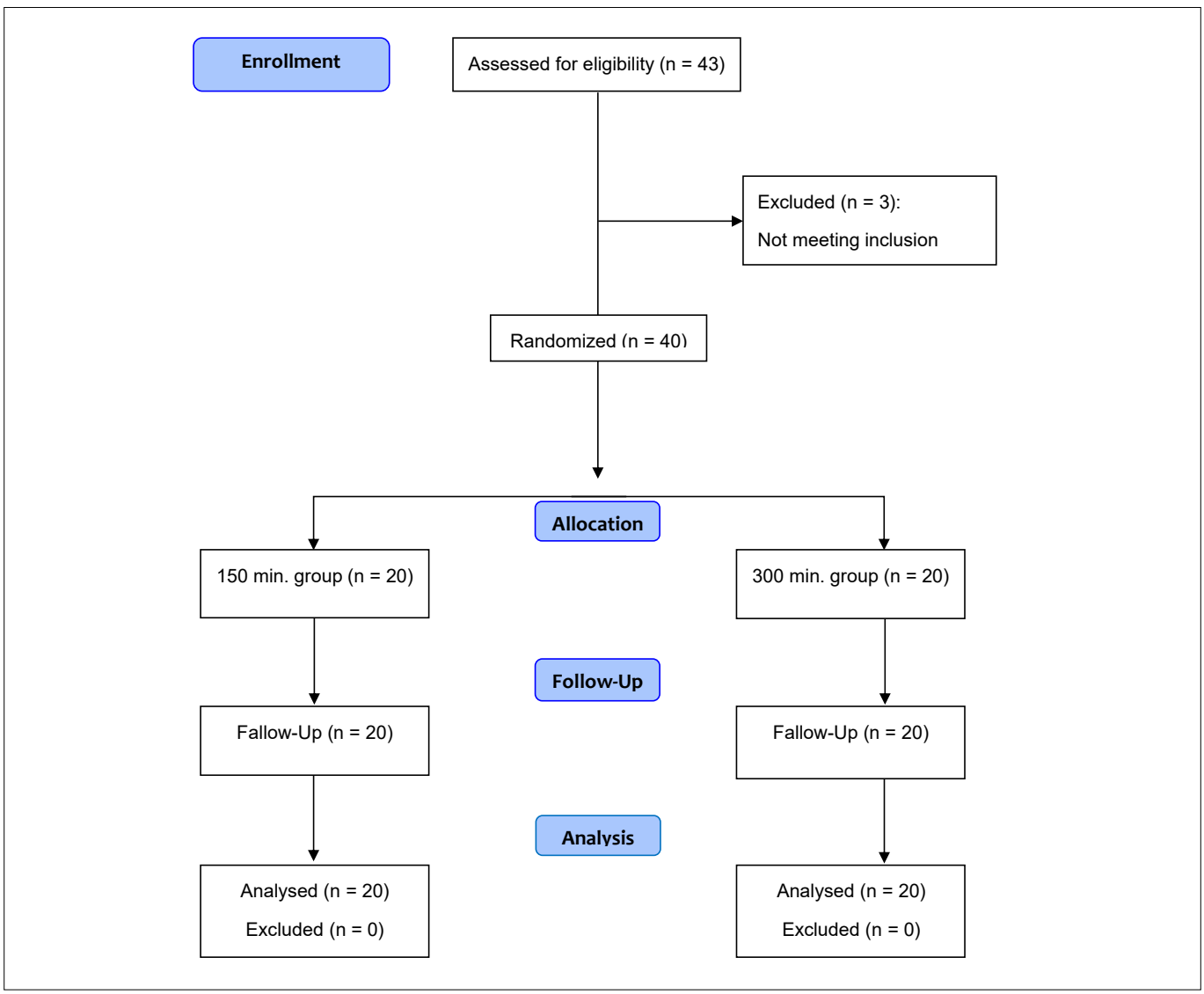

Figure 1. Flowchart.

not participated in training programs during the previous six months, they may have had low exercise tolerance, which would reduce their commitment. Therefore, the suggested durations could be performed continuously in each session or with minimal rest intervals (if necessary), as long as a minimum duration of 10 minutes was maintained in each effort period, thus maintaining the aerobic nature of the exercise.[22] Walking intensity and RPE[19,20] recording guidelines were the same as those recommended for the G150.[10,11]

Outcomes – blinded

The evaluations were performed by a third party who was unaware of the research content. Individuals could count on the presence of one or more companions/family members to perform the tests, and those who use mobility aids (canes/walkers) and/or assistive devices (orthotics and insoles) should maintain their use during assessments for safety and to reduce the risk of falling. All the tests were explained in advance by the researcher. The primary variables assessed were walking performance based on comfortable speed and walking endurance (distance walked in the 6MWT)[6] and functional mobility (time taken to complete the TUG test).[14,15]

Secondary variables included performance on a functional test of sitting and standing five times, and maximum walking speed. For tests that required precision from the examiner through time tracking (10 m sprint test,[6] TUG,[14,15] and FTSST[9]), the reliability of the intra-rater measurements was determined, which guaranteed an excellent intraclass correlation coefficient (ICC) for all variables (10 m sprint test:[6] ICC = 0.983; TUG:[14,15] ICC = 0.986; FTSST:[9] ICC = 0.953).

Gait performance was assessed using the 10-m sprint test, which consisted of measuring the time taken to walk 10 m in a straight line, starting from the starting position in a two-meter area and ending in a similar area.[6] This test is valid and reliable for measuring the CWS and maximum walking speed of individuals with chronic stroke.[7] Individuals performed three repetitions at the walking speed they considered comfortable (self-regulated) and three repetitions at the highest possible speed (maximum), with a one-minute recovery interval between each repetition. Prerepetition was performed to resolve any uncertainties.

Walking endurance was measured using the 6MWT.[6] The test consists of measuring the longest distance walked over a six-minute period using a 30-meter bounded space.[6] Only one repetition was performed, as this is a more physically demanding test. This test is also used to indirectly assess the aerobic capacity in individuals with various clinical conditions, including the elderly, healthy individuals, and individuals with stroke. This is reliable for measuring walking endurance in people with chronic stroke.[7] Before and after the 6MWT,[6] vital signs were measured using heart rate and blood pressure, and intensity was measured using the RPE.[19,20]

Functional mobility was measured using the TUG test.[14,15] The test measures the time taken to rise from a sitting position in a chair to an upright position, walk three meters, return, and sit down again. This is a valid and reliable test for measuring functional mobility in patients with chronic stroke.[7]

The ability to move from a sitting to a standing position was considered a secondary variable in this study. This was measured using the FTSST,[9] which requires the participants to stand and sit down five times in the shortest possible time, starting from a sitting position in a chair. The FTSST[9] is a valid and reliable measure of functional mobility based on the assessment of transfer from sitting to standing in individuals with stroke.[8] Three repetitions were performed with a one-minute recovery interval, and the mean time was recorded. Each participant performed one repetition to resolve any questions.

Sample size

The sample consisted of 40 adults (aged 18 years or older) with hemorrhagic and/or ischemic stroke of both sexes (31 men) who used or did not use devices to facilitate gait (orthoses and inserts) and mobility (cane and walker). The sample calculation was performed using GPower 3.1 software (Heinrich Heine University, Düsseldorf, Germany), considering repeated measures comparisons between factors (time and group) with a minimum effect size of 40%, observed power of 90% (1- $\beta = 0.90$), and index significance level of 5% (α of 0.05), resulting in a sample size of 36 individuals.[7] However, to account for potential sample loss throughout the process, 43 individuals were included, of which three were excluded based on the imposed criteria, resulting in a final sample of 40 individuals.

Statistical methods

We performed an intention-to-treat analysis[23] using SPSS version 24.0. The Shapiro–Wilk test was used to test the normality assumption of the variables. The t-test, chi-square test, and/or Fisher's exact test were used to compare descriptive statistics depending on the level of the variables. A generalized estimating equation model was used to compare the quantitative variables in each experimental group (G150 and G300) in the pre- and post-intervention situations.[24] Time and group were considered as independent fixed effect factors and Bonferroni post hoc test was used when necessary (significance level used was $P < 0.05$).

Effects of independent fixed factors and parameter estimates from generalized estimating equations were described using Wald comparison values (W-value: values > 1 indicate a significantly estimated probability), P value, and difference

of means (B value) with a 95% confidence interval (95% CI).[24] The effect size was also determined using Cohen' d for paired groups.[25]

For tests that required the precision of the examiner by timing (10 m sprint test,[6] TUG,[14,15] and FTSST[9]), the intra-rater reliability of the measurements was determined using the Wilcoxon test followed by Spearman's correlation and determination of the ICC. The two-way absolute agreement model was used for this calculation, with the mean of the three trials used as the criterion for time determination.[26,27] Reliability was interpreted as low (< 0.40), moderate (0.40 to 0.75), substantial (0.75 to 0.90), or excellent (> 0.90).[25]

RESULTS

The sample characteristics and exercise session records are in **Tables 1** and **2**. In the comparison carried out using the generalized estimating equation model (**Table 3**), it was determined that only the time factor was influenced by the proposed intervention, significantly modifying all dependent variables evaluated before and after the prescription of unsupervised walking. No significant differences were observed between the group factors and no significant interaction was found for the group × time interaction, indicating that G150 and G300 changed similarly.

Table 1. Sample characterization. Values are described as mean (± SD) or % (absolute number)

Variables	150 min. group (n = 20)	300 min. group (n = 20)
Age (years)	52 (± 14)	58 (± 10)
Sex (male)	80% (16)	75% (15)
Time since stroke (months)	44 (± 34)	39 (± 33)
Walking speed (m/s)	0.69 (± 0.22)	0.69 (± 0.25)
Mobility aid	70% (14)	65% (13)
Stroke type		
Ischemic	75% (15)	85% (17)
Hemorrhagic	25% (5)	15% (3)
Affected brain region		
Brain	75% (15)	80% (16)
Cerebellum	20% (4)	5% (1)
Stem	5% (1)	15% (3)
Spasticity [a]		
Degree 0	25% (5)	30% (6)
Degree 1	20% (4)	15% (3)
Degree 1+	35% (7)	40% (8)
Degree 2	20% (4)	15% (3)
Hemiparetic side		
Right	40% (8)	70% (14)
Left	60% (12)	30% (6)
Risk factors		
Systemic Arterial Hypertension	85% (17)	80% (16)
Dyslipidemias	60% (12)	85% (17)
Obesity	30% (6)	20% (4)
Smoking	25% (5)	15% (3)
Diabetes	20% (4)	20% (4)
Medications in use		
Antihypertensives	80% (16)	80% (16)
Antispastic	50% (10)	50% (10)
Hypoglycemic	15% (3)	20% (4)
ypocholesterolemia	10% (2)	70% (14)

[a] degree of spasticity in the lower limbs, as measured using the modified Ashworth scale. None of the comparisons showed significant differences (P ≥ 0.05).

Estimated mean for CWS increased for the G150 (from 0.69 m/s ± 0.22 m/s to 0.94 m/s ± 0.33 m/s) and for the G300 (from 0.69 m/s ± 0.25 m/s to 0.90 m/s ± 0.32 m/s), resulting in a large effect size for both (G150, Cohen d = 0.92; G300, 1.10). Performance on the TUG and 6MWT also improved, but the effect size was small. On the TUG, the time reduced for the G150 group from 12.65 s ± 8.38 s to 9.47 s ± 5.16 s (Cohen d = 0.47) and the G300 group from 11.58 s ± 7.12 s to 9.71 s ± 5.82 s (Cohen d = 0.29). For the 6MWT, the distance increased for the G150 group from 333.00 m ± 140.73 m to 404.30 m ± 163.17 m (Cohen d = 0.47) and the G300 group from 345.20 m ± 184.04 m to 413.25 m ± 152.43 m.

Regarding maximum walking speed, despite the improvement in performance for G150 (from 1.00 m/s ± 0.46 m/s to 1.27 m/s ± 0.57 m/s; Cohen d = 0.53) and G300 (from 0.98 m/s ± 0.40 m/s to 1.28 m/s ± 0.58 m/s; Cohen d = 0.61), the effect size was medium for both groups. Likewise, for the FTSST (G150: from 11.25 s ± 5.3 s to 8.10 s ± 2.35 s, Cohen d = 0.79; G300: 8.70 s ± 4.38 s, Cohen d = 0.55).

Table 2. Records made during exercise sessions

Variables	150 min. group (n = 20)	300 min. group (n = 20)
Borg Rating of Perceived Exertion (RPE) scale		
Light (< 11)	10% (2)	0
Moderate (11–14)	85% (17)	80% (16)
High (> 14)	5% (1)	20% (4)
Realized volume in relation to proposed		
Full (100%)	90% (18)	90% (18)
Partial 1 (80%–99%)	10% (2)	10% (2)
Partial 2 (< 80%)	0	0

RPE = Borg Rating of Perceived Exertion. None of the comparisons showed significant differences (P ≥ 0.05).

Table 3. Effects of independent factors and parameter estimates

Variables	Factors	W value[a]	P value[b]	B value[c]	95% CI
CWS (m/s)	Group	0.091	0.763	0.043	-0.111, 0.198
	Time	33.677	< 0.001*	-0.258	-0.397, -0.120
	Group × Time	0.269	0.604	0.051	-0.242, 0.141
MWS (m/s)	Group	0.034	0.854	-0.024	-0.106, 0.388
	Time	16.595	< 0.001*	-0.267	-0.424, -0.110
	Group × Time	0.490	0.484	0.078	-0.141, 0.298
TUG (s)	Group	0.061	0.804	-0.025	-0.276, 0.226
	Time	23.869	< 0.001*	0.176	0.114, 0.238
	Group × Time	0.408	0.235	0.113	-0.074, 0.300
6MWT (m)	Group	0.094	0.759	-0.022	-0.191, 0.148
	Time	73.638	< 0.001*	-0.180	-0.254, -0.106
	Group × Time	0.104	0.747	-0.014	-0.099, 0.071
FTSST (s)	Group	0.414	0.520	-0.072	-0.252, 0.108
	Time	96.300	< 0.001*	0.321	0.218, 0.420
	Group × Time	0.014	0.905	0.008	-0.122, 0.138

CWS = Comfortable walking speed; MWS = Maximum walking speed; TUG = Timed up and go test; 6MWT = 6-min walk test; FTSST = Five times sit to stand test.
[a] Comparison of means estimated by generalized estimating equations (Wald value).
[b] Significant difference (P < 0.05).
[c] Difference from estimated means with confidence interval (95% CI).
* P < 0.001.
[b,c] = Generalized estimating equations for longitudinal data analysis – time and group were considered independent fixed effect factors, and Bonferroni post hoc was used when necessary (Ballinger, 2024).[24]

DISCUSSION

Among the variables evaluated, CWS, which is an important parameter to characterize independent walking performance[28,29] and is also used to classify poststroke walking ability,[30] increased similarly in both groups (G150: 0.94 m/s; G300: 0.90 m/s), resulting in large effect size (Cohen d > 0.8).[25] Thus, the results of the present study demonstrated that even in an unsupervised manner, walking training of 150 or 300 minutes per week significantly increased the CWS of individuals to the point of becoming community walkers[31] limited to unlimited, thus contributing positively to their level of independence.[32]

Charalambous et al. suggested that the clinical significance of a CWS would only be achieved after 12 weeks of training.[33] However, in addition to using a weekly duration of 90 minutes, which is less than recommended for health benefits,[10,11] they walked on a treadmill combined with electrical stimulation of the ankle muscles. In the present study, clinical relevance was achieved with a large effect size for the same variable and in a shorter time period (eight weeks), with walking training performed on the ground in an unsupervised manner, and with a weekly duration of physical activity sufficient to provide health benefits.

Performance on the TUG,[14,15] an important test to assess functional mobility after stroke, improved in both groups after the intervention (G150: 9.7 s, effect size = 0.47; G300: 9.71 s, effect size = 0.29), but with little clinical relevance as the effect size was small.[25] Similarly, performance on the 6MWT,[6] although improved, was of little clinical relevance, with a small effect size (G150: 404.30 m, effect size = 0.47; G300: 413.25 m, effect size = 0.41).

Among the secondary variables, maximum walking speed, which measures the ability to walk quickly over short distances, showed a significant increase ($P < 0.001$) with a medium effect size in both groups. Performance on the FTSST[9] also improved significantly ($P < 0.001$), with a reduction in test performance time and average effect size for both groups, similar to that found for maximum walking speed. To date, no values of clinical importance have been found for these two variables, which would allow for comparisons with other training programs.

Maintaining a regular walking routine for eight weeks, even if unsupervised, may have provided a training overload capable of stimulating neuroplasticity, increasing the recruitment of motor modules, and improving muscle synergy.[34] Consequently, greater muscular synergy or synchronization of motor units may have contributed to increases in explosive strength, balance, and skills required in the tests performed and in everyday tasks.[32,34]

Another explanation for the benefits of walking could be related to the reduction in the co-activation time of the lower limb muscles, which would lead to better intramuscular coordination, as has already been shown in training with the same exercise.[35] Among these possible neural adaptations that occurred, the synchronization of motor units was perhaps the most prevalent with running training. This could also explain the greater performance gains in tests that mainly demand explosive strength (maximum walking speed and FTSST[9]) compared to the TUG[14,15] and 6MWT,[6] which predominantly demand other abilities, such as balance and resistance, respectively. Regarding the proposed protocols, moderate effort was most frequently reported by individuals in unsupervised training sessions, which is compatible with the intensity recommended in the literature.[10,11]

Furthermore, the individuals already had a high performance of functional mobility and walking endurance at the time of enrolment, with values higher than those of other studies for the TUG[14,15] and 6MWT,[6] respectively.[18] A possible explanation for this better baseline performance in the present study could be the fact that individuals had already participated in a post-stroke rehabilitation program, although it was not possible to quantify the previously spent rehabilitation time. This would also explain the smaller effect sizes for TUG[14,15] and 6MWT,[6] as the baseline performance was already high and little could change with the intervention performed.

Studies that used walking as an exercise in the training program and found improvements in gait performance and functional mobility used volumes close to or equal to 150 minutes per week,[18] but they used treadmills and/or close professional supervision. This distinguishes this study, which also found interesting results when walking training was performed on the ground and unsupervised.

The proposed two-weekly training duration improved all variables evaluated, including those of great clinical importance for CWS. Therefore, professionals involved in the rehabilitation of stroke patients may find that 150 minutes of weekly walking in a home/community setting is sufficient because it requires little daily time and keeps individuals physically active as recommended.[10,11]

CONCLUSION

Unsupervised walking was effective in improving the gait performance and functional mobility of individuals with chronic stroke regardless of the recommended weekly duration (150 or 300 minutes). Therefore, walking for 150 minutes a week may be sufficient to improve gait and functional mobility in individuals with chronic stroke who have already participated in rehabilitation programs.

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Postural assessment of children with congenital Zika syndrome and caregivers in the home environment: a cross-sectional pilot study

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ABSTRACT

BACKGROUND: Children with congenital Zika syndrome (CZS) present severe motor impairment that hinders their caregivers' positioning during activities of daily living (ADLs).

OBJECTIVE: To assess the posture of children with CZS and their caregivers during ADLs in the home environment.

DESIGN AND SETTING: A cross-sectional pilot study conducted in Campina Grande (PB), Brazil.

METHODS: Nine children with CZS (mean age = 36.77 ± 2.94 months) and their caregivers (n = 9, mean age = 27 years) were assessed. Data were collected at the support home of a center for children with microcephaly in Northeast of Brazil. For postural assessment, children and their caregivers were filmed while performing ADLs in the living room and kitchen of the support home.

RESULTS: During the environmental interaction, all children predominantly maintained a sitting position, exhibiting neck and trunk asymmetry; 77.8% (n = 7) showed inadequate postures with elevated arms and shoulders, and none maintained the ankles in a neutral position with supported feet. During feeding, 88.9% (n = 8) of children were positioned on the lap of caregivers, 88.9% (n = 8) exhibited neck and trunk asymmetry, 66.7% (n = 6) displayed inadequate upper-limb posture, and none maintained their ankles in a neutral position. During this activity, 66.7% (n = 6) of caregivers presented with trunk and neck asymmetry, 66.7% (n = 6) did not provide support for the upper limbs, and 55.6% (n = 5) did not maintain their knees flexed at 90°.

CONCLUSIONS: Children with CZS and their caregivers present with inadequate postures during ADLs in the home environment, which may represent health risks.

INTRODUCTION

Congenital Zika syndrome (CZS), which was initially described in 2016, is characterized by neurodevelopmental impairments due to intrauterine Zika virus infections.[1] Microcephaly is the primary and most evident clinical manifestation of CZS; nevertheless, children with this pathology may present with other neurological abnormalities such as juxtacortical calcifications, cortical malformations, ventriculomegaly, and cerebellar and brainstem hypoplasia.[2-5]

Upon physical examination, children with CZS often show craniofacial disproportions, occipital bone protrusion, closed fontanelles at birth, and excessive or folded scalp skin.[5,6] Other impairments become apparent with age, including severe intellectual and motor disabilities, altered muscle tone, irritability, intractable epilepsy, dysphagia, and anomalies in the visual and auditory systems.[5,7-9]

Neurological impairment in children with CZS may delay or impair motor development. Wheeler et al. (2018) assessed 47 children with CZS aged 16 months and reported that one child could maintain an upright position without support, whereas approximately 25% could roll or maintain a quadruped position without help.[10] Therefore, children with CZS often remain seated, lying down, or held by caregivers for long periods. By contrast, caregivers of children with CZS frequently experience musculoskeletal pain, which can compromise their quality of life.[2,11,12]

Analyzing the posture of children with CZS and their caregivers during activities of daily living (ADLs) is crucial for understanding the risk of osteoarticular deformities in children and musculoskeletal pain in caregivers, aiding in the selection of adequate therapeutic interventions. To date, the postures of children with CZS and their caregivers during ADLs have not been analyzed in detail. Performing this analysis in everyday environments can reveal difficulties experienced by children and caregivers.

OBJECTIVE

This study aimed to assess the posture of children with CZS and their caregivers during ADLs in the home environment.

METHODS

This cross-sectional pilot study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[13] guidelines. The study was developed by the Instituto Assistencial Professor Joaquim Amorim Neto (IPESQ) and the Center for Strategic Technologies in Health at the Universidade Estadual da Paraíba (UEPB). Data were collected in February and March 2020. Informed consent was obtained from all children's parents or legal guardians. All procedures were conducted in accordance with the Declaration of Helsinki, and the study was approved by the Institutional Review Board of Hospital Universitário Alcides Carneiro on February 21, 2020 (protocol number 26305819.2.0000.5182).

Sample

Children and their caregivers were recruited from a support center for children with microcephaly linked to the IPESQ in Campina Grande (PB), Brazil, using a non-probabilistic technique. Since 2015, this center has provided multidisciplinary care for children with CZS. The IPESQ health team comprises trained and experienced medical doctors, nurses, physical therapists, speech therapists, and occupational therapists.

Children assisted in this center are from several Brazilian states and other countries in Latin America and Africa. Thus, mothers reside in a support home while their children undergo rehabilitation interventions. When study was conducted a total of 71 children with CZS were assisted by the IPESQ, 24 of whom resided in the support home. All children evaluated in the present study resided in the support home when this study was conducted.

Samples were obtained using non-probability convenience sampling. Children were included in this study if they (1) had CZS diagnosed by reverse transcription polymerase chain reaction (RT-PCR) or imaging findings in the first months of life (computed tomography or magnetic resonance imaging), (2) were at least one year of age, and (3) required a caregiver to perform ADLs. Children who were not present for data collection and had osteoarticular deformities that could limit the sitting position were excluded.

Data collection and assessment procedures

First, general data on children (age, height, sex, and weight) and caregivers (age, sex, educational level, income, habitation, symptoms of Zika virus infection in pregnancy, trimester with Zika virus infection symptoms in pregnancy, type of delivery, and experience of caring for children with neurological impairment) were collected using IPESQ records and interviews with the caregivers. Motor impairment, ability to control the neck and trunk, and muscle tone were also assessed.

The Gross Motor Function Classification System (GMFCS), which classifies the level of motor impairment from level I (minimum impairment) to level V (severe impairment)[14-16], was employed to assess locomotion capacity and functionality according to age.

The Gross Motor Function Measure (GMFM) was used to assess the ability to control the neck and trunk. The GMFM assesses gross motor function during 88 tasks, with the score ranging from 0 (unable to initiate the task) to 3 (able to complete the task) for each task.[17] However, in this study, only item 22 (sitting on the carpet, supported on the chest by the therapist: raises the head in the midline, holds for 10 seconds) and item 23 (sitting on the carpet with the arms supported: maintains for 5 seconds) were used.[18]

The axial and proximal appendicular muscle tone of the children was assessed using the pull-to-sit maneuver, ventral suspension, scarf sign, and shoulder suspension.[19] For each maneuver, the children's responses were classified as positive (+, hypotonia) or negative (-, no hypotonia) according to the expected. Children who presented with a positive classification for at least one maneuver were considered to have axial hypotonia.

Due to resistance to passive movement, the proximal appendicular muscle tone was assessed using the Modified Ashworth Scale (MAS). The MAS classifies muscular resistance to passive movement into six levels: 0 (no increase in muscle tone) to 4 (rigid affected segment without movement).[20]

Postural assessment of caregivers and children during ADLs was performed after the physical examination. The assessment was conducted in the living room and kitchen of the support center for mothers, where caregivers and children performed most ADLs. In the living room, the postures of children were assessed while sitting during activities such as watching television, manipulating objects, and tasks stimulating the motor system and requiring interaction with the environment. In the kitchen, the postures of children and caregivers were assessed during feeding while considering task execution, positioning, and movement removal.

Films were recorded using a Canon EOS Rebel SL2 video camera positioned in front of the caregivers and children prior to the tasks. Thus, the researcher did not interact with the caregivers or children during filming to capture the postures as closely as possible to reflect daily reality.

The films were then analyzed according to a questionnaire adapted from the Brazilian version of the International Standard Organization (NBR ISO) 11,226, entitled "Ergonomics — Evaluation of static work postures – Rapid evaluation".[21] NBR ISO 11,226 establishes ergonomic recommendations for different work tasks, justifying the adaptation. Thus, we used the second stage of NBR ISO 11,226 by adapting 17 questions into 12–21 dichotomous questions (yes or no) for each body segment (neck, trunk, upper limbs, and lower limbs). The questions encompassed the essential elements for adequate posture in each task.

Regarding upper- and lower-limb assessments, the worst-positioned limb was considered the most overloaded limb. This analysis allowed for the identification of possible postural deviations, inadequacies in the use of equipment (e.g., positioning chairs), and health risks of postures. The absence of risk was considered when all questions in the questionnaire were answered with "yes." If any question presented the answer "no," the task was considered a health risk.

Statistical analysis

Initially, a specific database was created using REDCap software. Descriptive analysis was performed using measures of central tendency (mean) and dispersion (standard deviation) for continuous variables, such as the age, weight, and height of children and caregivers. In addition, absolute and relative frequencies of categorical variables (e.g., health risks from posture and microcephaly at birth) were determined.

RESULTS

Nine children aged 34–44 months (36.77 ± 2.94 months) were assessed, with five (55.5%) female children. Eight (88.8%) children were classified as GMFCS level V, and five (55.5%) had axial hypotonia and proximal appendicular hypertonia. All caregivers were mothers aged 23–35 years (27 ± 4.69 years), with three (33.3%) reporting a complete higher education (**Table 1**).

Postural assessment of children

During the environmental interaction activities, all children predominantly maintained a sitting position, exhibiting neck and trunk asymmetry. Seven children (77.8%) demonstrated anterior neck and trunk inclination. Regarding upper-limb posture, none maintained their elbows at a 90° angle, and seven exhibited inadequate postures with elevated arms and shoulders. The wrist showed a less inadequate posture, with only one child (11.1%) displaying a radial deviation. Lower-limb analysis revealed that none of the children maintained their ankles in a neutral position with supported feet, six children (66.7%) exhibited hip abduction, and five children (55.6%) showed internal hip rotation. **Table 2** presents the details of these findings.

Table 3 describes the criteria and results of postural assessments of the children during feeding. During feeding, eight children (88.9%) were positioned on the caregivers' lap, one child (11.1%) was in a wheelchair, and none were in a feeding chair. Analysis of images depicting the execution of this task revealed that eight children (88.9%) exhibited neck and trunk asymmetry, whereas seven children (77.8%) presented neck and trunk inclination. Six children (66.7%) displayed inadequate upper-limb posture, and all children had their elbows flexed at a 90° angle. As for lower limbs, none of the children maintained their ankles in the neutral position with their feet supported during feeding.

Postural assessment of caregivers

Six caregivers (66.7%) presented with trunk and neck asymmetry during feeding. All caregivers presented neck inclination, and seven (77.8%) presented trunk inclination. Caregivers also showed altered upper-limb positioning, such as arm elevation (n = 9), lack of support (n = 6), and no elbow flexion at 90° (n = 9). Regarding the lower limbs, no caregivers maintained their ankles in a neutral position with supported feet, and five caregivers (55.6%) did not maintain their knees flexed at 90° (**Table 4**).

Regarding the posture adopted for positioning or removing children from the feeding position, caregivers reported trunk inclination and shoulder elevation. Eight caregivers (88.9%) did not perform hip or knee flexion and no caregivers presented with lateral wrist deviation. The data related to this analysis are presented in **Table 5**.

DISCUSSION

In the present study, monitoring children with CZS during ADLs in a home environment allowed for the identification of inadequate postures in children and caregivers. Specifically, most children exhibited neck and trunk asymmetry and foot misalignment during the tasks. During feeding, caregivers frequently presented with postural inadequacies of the trunk and neck. In addition, most caregivers demonstrated postural inadequacies in all body segments during positioning and removal of children from the feeding position. The results presented here demonstrate the postural inadequacies experienced by children with CZS and their caregivers during ADLs. These postures may represent risks to children's and caregivers' health; however, this hypothesis should be investigated in future studies.

Motor impairment often hampers the ability to sit, stand, and perform ADLs independently.[22-24] The motor impairment of children with CZS has been extensively discussed in the literature since the description of the first cases.[8,23,24] Melo et al. reported that 81% of children with CZS had severe motor impairments, classified as GMFCS level V.[8] Similarly, in this study, children were classified as GMFCS levels IV and V, requiring help to perform ADLs.

Inadequate positioning, severe motor impairment, altered muscle tone, muscle weakness, impaired motor coordination, and excessive agonist or antagonist co-activation may cause secondary neuromotor complications (e.g., shortening and contractures) in children with neurological impairment.[25] High GMFCS levels accelerate these complications in children with CZS, who are also at risk of multiple contractures and postural inadequacies.[26,27] Likewise, in the children assessed in this study, impaired motor function and inadequate positioning during ADLs suggest an increased risk of developing secondary osteoarticular deformities, compromising motor function and quality of life of children and caregivers.

Casey et al. evaluated contractures in children with different GMFCS levels. In their study, children with GMFCS levels IV and V

Table 1. Characterization of children and caregivers

Variable	n (%)	Mean ± SD	Range
Characteristics of children			
Age (months)		36.26 ± 3.79	34–44
Sex			
Female	4 (44.4)		
Male	5 (55.5)		
Weight (kg)		11.54 ± 1.56	9–12.63
Height (cm)		90.27 ± 3.86	86–97
Microcephaly			
Yes	8 (88.8)		
No	1(11.1)		
GMFCS level			
IV	1 (11.1)		
V	8 (88.8)		
Item 22 GMFM			
1 – Initiate the task	1 (11.1)		
2 – Partially completes the task	2 (22.2)		
3 – Completes the task	6 (66.6)		
Item 23 GMFM			
0 – Unable to initiate the task	4 (44.4)		
3 – Completes the task	5 (55.5)		
Muscle tone classification			
No axial hypotonia and no proximal appendicular hypertonia	1 (11.1)		
No axial hypotonia and proximal appendicular hypertonia	3 (33.3)		
Axial hypotonia and proximal appendicular hypertonia	5 (55.5)		
Characteristics of caregivers			
Age (years)		27 ± 4.690	22–35
Weight (kg)		67.44 ± 11.640	53–86
Height (m)		1.56 ± 0.057	1.50–1.64
Educational level			
Complete high school	6 (66.6)		
Complete higher education	3 (33.3)		
Experience of caring (years)		7 ± 4.18	4–16
Income (*reais*)		646.91 ± 493.69	50–1.625
Habitation			
Urban area	8 (88.8)		
Countryside	1 (11.1)		
Symptoms of Zika virus infection in pregnancy			
Yes	8 (88.8)		
No	1 (11.1)		
Trimester with Zika virus infection symptoms in pregnancy			
First trimester	6 (66.6)		
Second trimester	2 (22.2)		
No symptoms	1 (11.1)		
Type of delivery			
Vaginal delivery	5 (55.5)		
Cesarean section	4 (44.4)		

GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; CZS = congenital Zika syndrome.

presented with contractures mostly in the knee joint, followed by those in the hip joint. This finding may be due to the long sitting time of these children.[27] However, the present study did not observe significant knee joint asymmetry, possibly because a detailed assessment of this joint was hindered as the children remained seated during the tasks.

Considering the risk of secondary complications related to positioning and identified inadequacies, addressing these postures is crucial in rehabilitation programs for children with CZS. In this sense, proper seating has been suggested as a strategy for normalizing muscle tone, reducing the influence of abnormal reflexes,

Table 2. Postural assessment of children during environmental interactions

Evaluation criteria	Yes n (%)	No n (%)
Assessment of neck and trunk		
Posture of the trunk and neck are symmetrical		9 (100)
Trunk flexion above 20°?	-	9 (100)
No trunk inclination?	2 (22.2)	7 (77.8)
No neck tilt?	2 (22.2)	7 (77.8)
Trunk remains supported?	2 (22.2)	7 (77.8)
Assessment of the most burdened upper limb		
No inappropriate arm postures?	2 (22.2)	7 (77.8)
No shoulder lift?	2 (22.2)	7 (77.8)
Arms raised below 20° without support?	4 (44.4)	5 (55.6)
Arms with elevation above 60° and with full support?	-	9 (100)
No extreme flexion and extension or rotation of the elbow?	2 (22.2)	7 (77.8)
Elbow flexed at 90°?	-	9 (100)
No extreme wrist deviation?	8 (88.9)	1 (11.1)
Assessment of the most burdened lower limb		
No kneeling and crouching posture?	9 (100)	-
No hip external rotation?	8 (88.9)	1 (11.1)
No hip internal rotation?	4 (44.4)	5 (55.6)
Hip remains at 90°?	6 (66.7)	3 (33.3)
Knee remains at 90°?	5 (55.6)	4 (44.4)
No knee abduction?	3 (33.3)	6 (66.7)
No knee adduction?	8 (88.9)	1 (11.1)
Ankle remains in neutral position and feet supported?	-	9 (100)

Table 3. Postural assessment of children during feeding

Evaluation criteria	Yes n (%)	No n (%)
Assessment of neck and trunk		
Posture of the trunk and neck are symmetrical	1 (11.1)	8 (88.9)
Trunk flexion above 20°?	-	9 (100)
No trunk inclination?	2 (22.2)	7 (77.8)
No neck tilt?	2 (22.2)	7 (77.8)
Trunk remains supported?	2 (22.2)	7 (77.8)
Assessment of the most burdened upper limb		
No inappropriate arm postures?	3 (33.3)	6 (66.7)
No shoulder lift?	7 (77.8)	2 (22.2)
Arms raised below 20° without support?	6 (66.7)	3 (33.3)
Arms with elevation above 60° and with full support?	9 (100)	-
No extreme flexion and extension or rotation of the elbow?	6 (66.7)	3 (33.3)
Elbow flexed at 90°?		9 (100)
No extreme wrist deviation?	9 (100)	-
Assessment of the most burdened lower limb		
No kneeling and crouching posture?	9 (100)	-
No hip external rotation?	7 (77.8)	2 (22.2)
No hip internal rotation?	8 (88.9)	1 (11.1)
Hip remains at 90°?	5 (55.6)	4 (44.4)
Knee remains at 90°?	5 (55.6)	4 (44.4)
No knee abduction?	6 (66.7)	3 (33.3)
No knee adduction?	8 (88.9)	1 (11.1)
Ankle remains in neutral position and feet supported?	-	9 (100)

Table 4. Postural assessment of caregivers during feeding

Evaluation criteria	Yes n (%)	No n (%)
Assessment of neck and trunk		
Posture of the trunk and neck are symmetrical	3 (33.3)	6 (66.7)
Trunk flexion above 20°?	-	9 (100)
No trunk inclination?	2 (22.2)	7 (77.8)
No neck tilt?	-	9 (100)
Trunk remains supported?	5 (55.6)	4 (44.4)
Assessment of the most burdened upper limb		
No inappropriate arm postures?	-	9 (100)
No shoulder lift?	4 (33.3)	6 (66.7)
Arms raised below 20° without support?	4 (33.3)	6 (66.7)
Arms with elevation above 60° and with full support?	-	9 (100)
No extreme flexion and extension or rotation of the elbow?	6 (66.7)	3 (33.3)
Elbow flexed at 90°?	-	9 (100)
No extreme wrist deviation?	7 (77.8)	2 (22.2)
Assessment of the most burdened lower limb		
No kneeling and crouching posture?	9 (100)	-
No hip external rotation?	6 (66.7)	3 (33.3)
No hip internal rotation?	8 (88.9)	1 (11.1)
Hip remains at 90°?	5 (55.6)	4 (44.4)
Knee remains at 90°?	4 (44.4)	5 (55.6)
No knee abduction?	5 (55.6)	4(44.4)
No knee adduction?	8 (88.9)	1 (11.1)
Ankle remains in neutral position and feet supported?	-	9 (100)

Table 5. Postural assessment of caregivers during laying and removal of the child from feeding posture

Evaluation criteria	Yes n (%)	No n (%)
Assessment of neck and trunk		
Are trunk and neck symmetrical?	3 (33.3)	6 (66.7)
Trunk flexion below 20°?	3 (33.3)	6 (66.7)
No trunk hyperextension when removing the child?	3 (33.3)	6 (66.7)
No trunk inclination?	-	9 (100)
No neck tilt?	4 (44.4)	5 (55.6)
Flexion of legs and keep torso straight when removing the child?	1 (11.1)	8 (88.9)
Assessment of the most burdened upper limb		
No inappropriate arm postures?	-	9 (100)
No shoulder lift?	-	9 (100)
No extreme flexion and extension?	8 (88.9)	1 (11.1)
No extreme wrist deviation?	6 (100)	-
Assessment of the most burdened lower limb		
No kneeling and crouching posture?	6 (100)	-
Flexion of the knees and hips when removing the child?	1(11.1)	8 (88.9)

improving motor control and functionality, ensuring skin integrity, and preventing the development and emergence of deformities.[28] Despite the wide range of adaptive equipment available in the market to promote positioning and functionality for children with postural control deficits, most children in this study were fed at the laps of caregivers. This observation may be linked to the socioeconomic conditions of the mothers (Sa et al.), considering the cost of equipment.[29]

Since the Zika virus infection epidemic, most mothers of children with CZS are young and have low income.[29] Over the years, this situation has worsened because many women need to abandon paid work to care for their children or have been abandoned by their partners. Moreover, mothers of children with CZS are often the only ones responsible for supporting and caring for their children.[29] Caring for children with physical disabilities broadly affects caregivers' quality of life. Previous studies have described the impact

on the mental and physical health of mothers of children with CZS, especially due to the dependence of children in performing ADLs.[30,31]

A study conducted on 63 mothers of children with CZS reported musculoskeletal pain in 93.7% of mothers, with the lower back, thoracic, and cervical spine having the highest incidence of pain. The study demonstrated that pain complaints were directly related to lower scores on the quality-of-life assessment.[11] Moreover, inadequate postures adopted by mothers may be associated with the musculoskeletal pain reported in other studies. Furthermore, this indicates that caring for children with CZS overlaps with the mothers' health, which is impaired by the lack of auxiliary devices and health education strategies. Thus, there is a need to implement health education strategies involving the daily positioning of mothers and children to reduce health risks.

This study has several limitations. First, the sample size and investigated tasks were small. However, they allowed for maximum similarity between the daily lives of the caregivers and the environment. Second, the assessment procedure (film analysis) was subjective; nonetheless, this limitation was minimized by using trained evaluators and the same evaluator for all analyses.

By contrast, this study has strength in that it evaluated children with CZS in a familiar environment, as human performance cannot be analyzed in isolation from environmental conditions. ADLs depend on multiple factors related to the individual, the environment, and the task.[32]

These findings highlight the need for further research using larger sample sizes and health education strategies to correctly positioning children and caregivers during ADLs. Moreover, low-cost and accessible assistive devices are essential to ensure adequate positioning of children and caregivers, reducing health risks during ADLs.

CONCLUSION

Postural analysis of children with CZS and their caregivers revealed inadequate postures related to improper positioning of children. By repetition, children may develop secondary osteoarticular deformities, compromising their motor function and quality of life and increasing health risks. Additionally, all caregivers could not maintain adequate postural alignment, potentially increasing health risks.

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Determinants of mortality risk in older adults from the ELSIA study: a prospective cohort study

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ABSTRACT

BACKGROUND: This study investigated factors that may determine longevity in older adults, aiming to prolong their life expectancy and improve projections from before the coronavirus disease 2019 pandemic.

OBJECTIVE: To identify risk factors for mortality in older Brazilian adults.

DESIGN AND SETTING: A prospective cohort study, part of the *Estudo Longitudinal de Saúde do Idoso de Alcobaça*.

METHODS: This study included 332 older adults of both sexes who were followed up for over five years (2015–2020). Vital status was determined via telephone follow-up, information provided by family members, and death certificates. To identify the sociodemographic, health, functional, and behavioral factors associated with mortality risk among older adults, Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: The risk factors for mortality among older adults included the number of people living with them (HR = 1.22; 95%CI = 1.07–1.38) and the number of prescribed drugs (HR = 1.15; 95%CI = 1.00–1.32). Factors associated with a lower risk of mortality were greater time spent in physical activity (HR = 0.99; 95%CI = 0.90–0.99) and greater hip circumference (HR = 0.95; 95%CI = 0.31–0.99).

CONCLUSIONS: Sociodemographic, health, functional, and behavioral factors are determinants of mortality risk among older adults. Regular screening of the older adult population should be conducted to assess their general health status, allowing for more appropriate interventions to increase their quality of life and improve aging.

INTRODUCTION

The global older adult population is rapidly increasing, a trend that, coupled with consistent declines in birth rates, has shifted the global age pyramid.[1] Projections indicate that the older adult population will triple by 2050, representing approximately 16% of the global population.[1] In Brazil, the number of older adults is expected to grow by 56% over a 12-year period (2010–2022), with the median age increasing by six years to reach 35 years.[2]

Conversely, the coronavirus disease 2019 (COVID-19) pandemic led to a significant number of deaths, particularly among older adults aged ≥ 60 years and individuals with pre-existing medical conditions, disrupting previously established projections.[3,4] This resulted in a reduced life expectancy at birth in several countries,[5] with some, including Brazil, experiencing mortality rates exceeding 50%.[6]

Among the factors affecting mortality risk in older adults, sociodemographic factors such as age, marital status, and family structure are particularly significant.[7,8] Identifying and explaining sex differences in mortality risk by marital status is crucial, as the impact of living alone versus living with a partner can differ between males and females.[8] Health-related aspects, such as the emergence and progression of chronic diseases[9] or the number of drugs ingested,[10-12] also play a role in mortality risk by affecting metabolism and reducing longevity. Functional aspects, such as physical performance and independence, are additional factors that can affect mortality risk.[13,14] Behavioral factors, including regular physical activity and time spent in sedentary behaviors, also contribute to mortality risk.[15-18] These elements have been identified as determinants of mortality risk and are instrumental in understanding the complex interactions between lifestyle and health outcomes in older adults.[15-18]

Consequently, identifying factors that may serve as determinants of longevity in older adults is essential. Avoiding such risk factors and encouraging protective factors are important for

extending life expectancy and improving projections established before the emergence of the COVID-19 pandemic,[3,4] particularly among populations with low developmental indices.

OBJECTIVE

This study aimed to identify the risk factors for mortality among participants of the *Estudo Longitudinal de Saúde do Idoso de Alcobaça* (ELSIA). We hypothesized that sociodemographic, health, functional, and behavioral factors may determine mortality risk among older adults, thereby affecting their longevity.

METHODS

Ethical procedures

This study was approved by the Human Research Ethics Committee of the Universidade Federal do Triângulo Mineiro (Ordinance 966.983/2015, February 27, 2015) and the Universidade do Estado da Bahia (Ordinance 3.471.114/2020, July 26, 2019). All protocols and procedures were conducted in accordance with the principles of the Declaration of Helsinki and Resolution No. 466/12 of the Brazilian Ministry of Health. All participants provided signed informed consent prior to participation.

Study design and participants

This study is an excerpt from the ELSIA study, a prospective population-based cohort study that used survey methods and physical performance tests. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The baseline study, conducted between June and September 2015, included a sample of 473 older adults of both sexes, aged ≥ 60 years, who were registered with the family health strategy in the municipality of Alcobaça, a program aimed at enhancing and solidifying Primary Care in Brazil, following the principles of the Unified Health System. This information has been previously described by Galvão et al.[19] The follow-up continued for five years, between January and February 2020, with older adults invited to participate in the second wave of the research.

The inclusion criteria were signing an informed consent form, being registered with the family health strategy, and residing in the community. The exclusion criteria included scores ≤11 points on the Mini-Mental State Examination, indicating cognitive impairment;[20,21] experiencing severe difficulty with visual and/or hearing acuity; requiring the use of a wheelchair; having severe sequelae from a cerebrovascular accident with localized loss of strength; or having a terminal illness. A comprehensive overview of the participant descriptions, attrition rates, recruitment strategies, and other variables investigated can be found in previous studies.[22]

Mortality

Vital status was determined through telephone monitoring, information provided by family members, including death certificates; data obtained from the Civil Registry Office of Natural Persons of Alcobaça; and public consultations on the website of the Court of Justice of the State of Bahia. To calculate the survival time, the follow-up period was defined as the time elapsed from the beginning of the survey until death, censoring, or the end of the second phase (February 29, 2020).

Sociodemographic aspects

The assessed sociodemographic characteristics included age, income, sex (male or female), which was used as an adjustment factor in the model, and the number of people living in the same house as the participant.

Health aspects

The evaluated health aspects included the total number of hospitalizations and falls recorded in the 12 months preceding the assessment, the number of prescribed drugs, and the presence of diseases (< 2 and ≥ 2), assessed from a list of diseases proposed by the World Health Organization in the 10th revision of the International Classification of Diseases.[23]

Functional and behavioral aspects

Body mass was measured using a Wiso digital scale (W721) with a capacity of 180 kg and a precision of 0.100 g and 0.1 cm. The circumferences of the arm, thigh, and calf were also evaluated using standardized measurements on the participants' right side. Hip circumference was measured at the point of the greatest prominence in the region. All evaluations were performed using a flexible and inelastic measuring tape (Lange-TBW, Cambridge, Massachusetts, United States) 2 m in length, graduated in centimeters, and subdivided into millimeters.[24]

Disability in basic daily living activities was evaluated using the Katz scale, which has been adapted for the older Brazilian adult population.[25] The scale ranges from 0 to 12 points. For the analyses, the participants were dichotomized into independent (0 points) and dependent (≥ 1 point). Disability in instrumental activities of daily living was assessed using the Lawton and Brody Scale, which has also been adapted for older adult populations in Brazil.[26] The scale ranges from 0 to 14 points. For analyses, participants were dichotomized into independent (≥ 11 points) and dependent (< 11 points) groups.

Physical function was assessed using the Fullerton Functional Fitness Test,[27] with percentile distributions adopted as cutoff points.[28] The muscular strengths of the upper and lower limbs were evaluated using two tests: the elbow flexion test, using a 2 kg load for females and a 3 kg load for males, which involved older

adults performing as many elbow flexions as possible within 30 seconds. The chair sit-and-stand test required participants to sit down and stand up from a chair without hand support as many times as possible within 30 s. The number of completed repetitions was recorded to analyze strength. For categorical data analysis, percentiles ≤ P25 were considered indicative of lower strength, whereas percentiles > P25 indicated higher strength.

A stationary walking test was used to evaluate aerobic endurance. The older adult participants were instructed to raise their knees to a predetermined height as many times as possible within 2 min. For the analysis of categorical data, the participants were classified based on percentiles, with ≤ P25 indicating lower endurance and > P25 indicating higher endurance.

Agility and dynamic balance were assessed using the 2.44-meter timed up and go test. The test began with the participants seated; when instructed, they walked as quickly as possible to a cone, circled it, and returned to their seats. For the analysis of categorical data, the participants were classified based on percentiles, with ≤ P75 representing slower times and > P75 indicating faster times.

Physical activity (PA) and exposure time to sedentary behavior were assessed using the International Physical Activity Questionnaire.[29,30] PA was evaluated based on moderate-to-vigorous-intensity activity (MVPA) measured in 10-minute bouts. Sedentary behavior was defined as the time spent sitting, lying, or reclining during waking hours. This was assessed using questions about sitting time on a typical weekday ("How much total time do you spend sitting during a weekday?") and a typical weekend day ("How much total time do you spend sitting during a weekend day?"). The total time spent sitting in minutes per day was calculated from the weighted average of the sitting time on weekdays and weekends:

Total time spent sitting = [(sitting time on a weekday × 5) + (sitting time on a weekend day × 2)]/7.[31]

Frailty syndrome was assessed using the adapted version of Fried et al.'s frailty phenotype,[32] which considers four components: unintentional weight loss, exhaustion, decreased muscle strength, and slow gait speed. Unintentional weight loss was assessed by asking, "In the last year, have you lost more than 10 pounds unintentionally (i.e., without dieting or exercising)?" Participants who answered affirmatively were considered to meet this criterion for frailty. Exhaustion was identified through two questions from the Geriatric Depression Scale (GDS-15), translated and validated for the Brazilian population:[33] "Did you stop doing many of your activities and interests?" and "Do you feel full of energy?" A positive answer to the first question and/or a negative answer to the second question indicated exhaustion or fatigue, thus meeting this criterion for frailty.

A decrease in muscle strength was assessed based on handgrip strength measured in kilograms of force (kgf) using an SAEHAN hydraulic dynamometer (Saehan Corporation SH5001, Korea). The participants were instructed to remain standing with their elbows extended, press the handle of the dynamometer with the highest force possible using their dominant hand, and hold it for 6 s (self-reported by the participant). Three measurements were obtained, with a 1-minute recovery time between attempts. The best performance was used for the analysis.[32]

Walking speed was measured using the 4.57-meter walk test, adjusted for sex and height.[32] Older adults who scored above the cutoff point for the walking test and those who were unable to perform it because of physical limitations met this criterion for frailty.

Frailty was measured dichotomously: older adults who scored 0, 1, or 2 points were classified as robust, while those who scored ≥ 3 points were classified as frail.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, New York, United States), and JASP version 0.18.3.0 (University of Amsterdam, Amsterdam, Netherlands). Data normality was assessed using the Kolmogorov–Smirnov test.

Descriptive statistics, including absolute and relative frequencies, medians, and interquartile ranges (IQRs), were used to examine the samples. To compare participants based on their vital status, the chi-square and Mann–Whitney U tests were used for categorical and continuous variables, respectively. Median differences expressed as Δ were calculated for continuous variables according to the vital status. Effect sizes were calculated using rank biserial correlation (rB) and the respective 95% confidence intervals (CIs), with values trivial (< 0.10), small (0.10–0.29), medium (0.30–0.49), or large (≥ 0.5).[34]

To identify the risk factors for mortality, crude and multivariate analyses were performed with hazard ratio (HR) estimates using Cox proportional hazards regression. Bivariate models were constructed for each independent and response variable (mortality). Variables with $P < 0.05$ were considered candidates for inclusion in the hierarchical multivariable model. Variables were introduced into blocks in the model, which was controlled for age, sex, and income. Block 1 contained sociodemographic aspects, such as the number of people living in a household. Block 2 included health aspects, such as the number of hospitalizations, falls, and drug use. Block 3 encompassed functional aspects (basic activities of daily living, instrumental activities of daily living, aerobic endurance, upper limb strength, lower limb strength, agility, dynamic balance, and frailty syndrome), anthropometric aspects (body mass, arm, hip, thigh, and calf circumferences), and behavioral aspects (PA and sedentary behavior). A significance level of 5% and 95%CI were used to calculate HRs.

RESULTS

During the follow-up of the 473 older adults included in the baseline study, 105 could not be located, and 36 had moved to other cities, resulting in the exclusion of 141 participants. Of the 332 participants who returned, 59 died and 273 were alive. The second phase occurred between January and February 2020. The characteristics of older adults are shown in **Figure 1**; additional information is described in previous studies.[22]

Among the participants included in the present study, 121 were male (36.4%), and 23 (19%) died during the follow-up period. Of the 211 female participants (63.6%), 36 (17.1%) had died. The mean age of the living participants was 69.7 ± 7.6 years, whereas the mean age of those who died was 76.9 ± 9.6 years. The average income of the surviving and deceased participants was 2,089 ± 3,492 Brazilian reais and 2,089 ±1,949 Brazilian reais, respectively.

Table 1 describes the categorical variables for the vital status of the study participants. Among the participants who died during the study, the highest prevalence was observed in individuals with more diseases, those who were dependent, and those with worse performance on the physical tests. Although a higher absolute number of deaths occurred among non-frail participants, the percentage of deaths was significantly higher in the frail group.

The quantitative data and their relationships with vital status are presented in **Table 2**. Except for the number of hospitalizations and falls, all other variables differed according to the vital status. The observed effect sizes ranged from trivial (d = -0.094) to medium (d = 0.401).

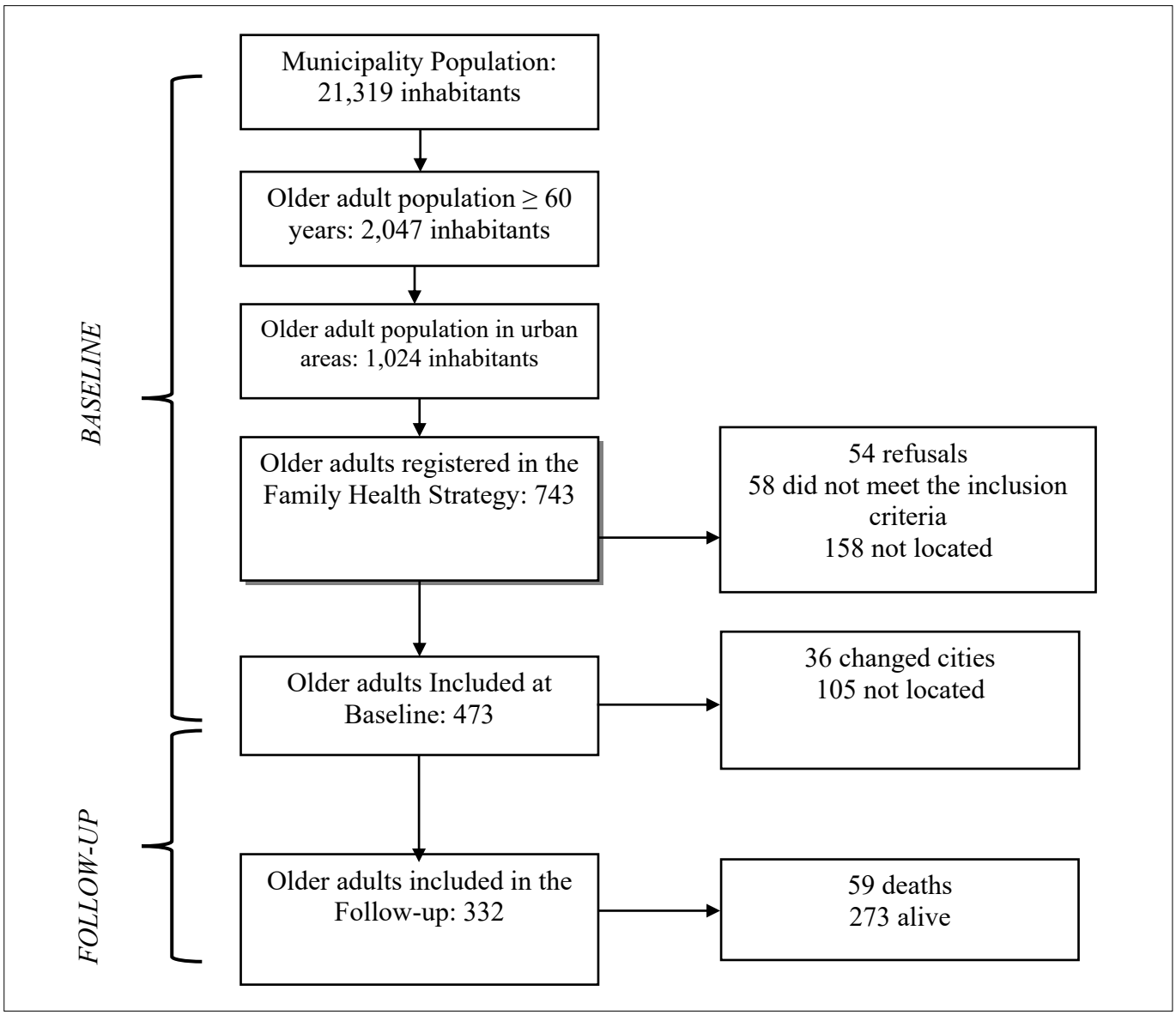

Figure 1. Flowchart of the study participants.

The risk factors analyzed using Cox regression analysis are presented in **Table 3**. After adjusting for sex, age, and income, the identified risk factors for mortality were the number of people with whom the older adult lived (HR = 1.22; 95%CI = 1.07–1.38) and the number of prescribed drugs consumed (HR = 1.15; 95%CI = 1.00–1.32). Conversely, greater time spent in PA (HR = 0.99; 95%CI = 0.90–0.99) and greater hip circumference (HR = 0.95; 95%CI = 0.31–0.99) were protective factors against mortality risk.

Table 1. Comparisons of qualitative variables among *Estudo Longitudinal de Saúde do Idoso de Alcobaça* (ELSIA) study participants according to vital status

Variables	Alive	Deceased	P
	n (%)	n (%)	
Diseases			
< 2	145 (87.3)	21 (12.7)	0.015
≥ 2	128 (77.1)	38 (22.9)	
Basic activities of daily living			
Independent	222 (85.4)	38 (14.6)	0.004
Dependent	51 (70.8)	21 (29.2)	
Instrumental activities of daily living			
Independent	194 (89.4)	23 (10.6)	< 0.001
Dependent	79 (68.7)	36 (31.3)	
Aerobic endurance			
Good	205 (89.5)	24 (10.5)	< 0.001
Moderate or poor	55 (67.9)	26 (32.1)	
Upper limb strength			
Good	193 (88.9)	24 (11.1)	< 0.001
Moderate or poor	70 (70.7)	29 (29.3)	
Lower limb strength			
Good	191 (89.7)	22 (10.3)	< 0.001
Moderate or poor	74 (69.8)	32 (30.2)	
Agility and dynamic balance			
Good	207 (89.2)	25 (10.8)	< 0.001
Moderate or poor	59 (67.8)	28 (32.2)	
Frailty syndrome			
Not fragile	249 (86.2)	40 (13.8)	< 0.001
Fragile	17 (54.8)	14 (45.2)	

DISCUSSION

This study aimed to identify the risk factors for mortality among the ELSIA participants. The identified risk factors included the total number of people and older adults living with the participants and the total number of medications consumed. Additionally, hip circumference and PA were also associated with mortality. These findings confirmed our hypothesis that sociodemographic, health, functional, and behavioral factors can determine mortality risk among older adults, thus affecting their longevity.

Among the sociodemographic conditions associated with mortality among older adults, the only variable that remained significantly associated with the risk of mortality, even after model adjustment, was the number of people living in the same household, with a 22% increase in mortality risk. These findings differ from those reported previously, demonstrating that living with a partner, can lower the risk of death compared to living alone.[7,8,35]

Being married can reduce mortality risk, depending on sex and age group.[7,8] A study investigating the role of living arrangements on mortality risk among approximately 54,000 European older adults aged ≥ 50 years observed higher mortality risks among individuals who lived alone. Men who lived with people other than their partners exhibited a higher risk of mortality compared with those who lived with a partner.[7] This finding aligns with those of other studies reporting that divorced or single males tend to have worse health outcomes compared with single females, suggesting that marital status may have a protective effect against mortality risk and may be linked to psychological factors, although the quality of relationships must also be considered.[35]

A cohort study conducted among older Japanese adults investigated the associations between family relationships in various domestic contexts, including the functional dimensions of support

Table 2. Comparison of quantitative variables among *Estudo Longitudinal de Saúde do Idoso de Alcobaça* (ELSIA) study participants according to vital status

Variables	Median (IQR)		Δ	P	*rB* (95% CI)
	Alive	Deceased			
Number of people	3.0 (2.0)	3.0 (3.0)	–0.93	0.088	-0.137 (-2.29 to 0.02)
Number hospitalization	3.0 (2.0)	3.0 (3.0)	–0.30	0.086	-0.094 (-0.25 to 0.06)
Number of falls	0.0 (0.0)	0.0 (0.0)	–0.39	0.061	-0.125 (-0.28 to 0.03)
Number of drugs	0.0 (1.0)	0.0 (1.0)	–1.15	< 0.001	-0.291 (-0.43 to -0.13)
Body mass (kg)	2.0 (3.0)	3.0 (3.0)	5.79	0.0021	0.195 (0.03–0.34)
Arm circumference (cm)	66.3 (19.3)	63.0 (21.0)	2.20	< 0.001	0.309 (0.15–0.45)
Hip circumference (cm)	29.6 (5.3)	27.5 (6.0)	4.62	< 0.001	0.285 (0.12–0.42)
Thigh circumference (cm)	99.0 (12.8)	93.7 (11.8)	4.26	< 0.001	0.323 (0.16–0.46)
Calf circumference (cm)	34.9 (5.0)	33.0 (4.6)	2.08	< 0.001	0.326 (0.17–0.46)
Physical activity (min/week)	200.0 (475.0)	10.0 (205.0)	260.84	< 0.001	0.401 (0.25–0.52)
Sedentary behavior (min/day)	395.7 (202.1)	480.7 (237.2)	–84.36	< 0.001	-0.275 (-0.41 to -0.11)

IQR = interquartile range; Δ = medium difference; CI = confidence interval; rB = rank biserial correlation.

Table 3. Risk factors for mortality among *Estudo Longitudinal de Saúde do Idoso de Alcobaça* (ELSIA) study participants

Variables	Raw analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Block 1–Sociodemographic aspects				
Number of people	1.19 (1.08–1.31)	< 0.001	1.22 (1.07–1.38)	0.002
Block 2–Health aspects				
Number of hospitalizations	1.37 (1.11–1.69)	0.003	1.19 (0.92–1.54)	0.251
Number of falls	1.15 (1.01–1.31)	0.025	1.19 (0.85–1.78)	0.181
Number of drugs	1.16 (1.07–1.27)	< 0.001	1.15 (1.01–1.32)	0.041
Block 3–Functional, anthropometric, and behavioral aspects				
Body mass	0.97 (0.95–0.99)	0.004	1.04 (0.99–1.09)	0.055
Arm circumference	0.88 (0.83–0.95)	0.001	0.97 (0.85–1.13)	0.700
Hip circumference	0.97 (0.95–0.99)	0.004	0.95 (0.31–0.99)	0.017
Thigh circumference	0.91 (0.87–0.95)	< 0.001	0.98 (0.90–1.08)	0.772
Calf circumference	0.86 (0.79–0.93)	< 0.001	0.88 (0.76–1.01)	0.077
Basic activities of daily living		0.002		0.826
Independent	1		1	
Dependent	2.28 (1.33–3.91)		0.91 (0.42–1.98)	
Instrumental activities of daily living		< 0.001		0.645
Independent	1		1	
Dependent	3.28 (1.94–5.56)		0.82 (0.36–1.87)	
Physical activity	0.99 (0.99–0.99)	0.001	0.99 (0.98–0.99)	0.045
Sedentary behavior	1.00 (0.99–1.00)	< 0.001	0.99 (0.99–1.00)	0.618
Aerobic endurance		< 0.001		0.250
Good	1		1	
Moderate or poor	3.72 (2.12–6.52)		1.57 (0.72–3.42)	
Upper limb strength		< 0.001		0.737
Good	1		1	
Moderate or poor	2.96 (1.71–5.10)		1.13 (0.54–2.38)	
Lower limb strength		< 0.001		0.746
Good	1		1	
Moderate or poor	3.50 (2.02–6.07)		1.14 (0.50–2.57)	
Agility and dynamic balance		< 0.001		0.097
Good	1		1	
Moderate or poor	3.69 (2.14–6.37)		2.10 (0.87–5.05)	
Frailty syndrome		< 0.001		0.814
Not fragile	1		1	
Fragile	3.04 (1.77–5.22)		0.91 (0.42–1.98)	

Adjusted for sex, age, income, and the presence of diseases. HR = hazard ratio; CI = confidence interval.

provided and received from children. The study identified a higher mortality rate among participants who received more support from their children (HR = 1.07), while those who provided more support to their children had a lower mortality rate (HR = 0.88) despite the unique social context in Japan.[14] Similarly, we hypothesized that the number of people living in the same house may be a risk factor based on the concept of independence, as a greater number of individuals living with older adults may hinder their ability to carry out basic and routine activities because of concerns and overprotection from younger family members, including children and grandchildren.

Physical and functional independence is crucial for the better quality of life and longevity of older adults. Galvão et al.[13] identified a mediating factor between functional performance and basic activities of daily living based on PA practice for survival time in an older adult population, suggesting that better scores on these variables are associated with greater longevity.

In this study, the number of medications was associated with a 15% increase in mortality risk, reflecting the impact of polypharmacy, commonly defined as the use of multiple medications.[10] Individuals with multiple comorbidities often take several medications concurrently, which can lead to inappropriate prescribing and various medication-related issues, including falls, fractures, kidney failure, increased frailty risk, decreased quality of life, hospitalizations, and, ultimately, increased mortality risk.[11] In their investigation of > 3 million older adults aged ≥ 65 years who continuously used at least one medication, Chang et al.[10] observed linear associations between mortality risk and hospitalizations among

older adults, even in subgroup analyses by sex and age. Another study involving 1,258 older adult aged ≥ 60 years reported a 77.2% survival rate among participants with polypharmacy (≥ 5 medications), compared with 85.5% among those taking < 4 medications.[36]

Although isolating the number of medications as an independent factor is difficult, as it often correlates with the number of pre-existing conditions, polypharmacy itself poses potential risks, even though medications are prescribed to improve health.[9,10] The findings of this study underscore the risks of polypharmacy and the critical need for careful and appropriate prescribing practices, along with strategies to minimize polypharmacy in the geriatric population.[10] Alternatives, such as non-pharmacological approaches, including regular PA, should be prioritized whenever possible to mitigate these risks.

PA is a modifiable behavioral factor that is crucial for longevity. In the present study, PA was found to be a protective factor against mortality (HR = 0.99). Although this value appears low, regular exercise reduces the risk of mortality in older adults,[16,37] regardless of sedentary time.[16,17] Ekelund et al.[17] demonstrated that regularly practicing MVPA for 60–75 min/day reduces the risk of mortality, regardless of sedentary time. Similarly, Stamatakis et al.[16] reported that ≥ 300 min of MVPA eliminated the mortality risks associated with sedentary time.

In the present study, hip circumference was a modifiable factor associated with reduced mortality risk. We observed a 5% lower risk of mortality among individuals with a larger hip circumference, consistent with other studies reporting inverse associations between hip circumference and mortality risk.[38] For instance, a study of 10,767 participants reported that a smaller hip circumference was a risk factor for diabetes and coronary artery disease.[39] However, a study that monitored changes in hip circumference over six years and assessed the risk of mortality observed that lower baseline hip circumference was a risk factor regardless of body mass index and waist circumference, but observed no associations with changes in hip circumference over time.[40] These contrary results suggest the need for further studies to explore whether circumference measurement is the optimal method for cardiovascular disease screening. Additionally, normative values should be developed similar to those established for body mass index, waist-to-hip ratio, and waist-to-height ratio to guide the interpretation of hip circumference and its association with various functional and physical outcomes.

Limitations, strengths, and practical applications

Our study had some limitations, including the use of subjective measures that could introduce bias. However, this was mitigated through prior training of the data collection team, resulting in a sample loss of approximately 30%. Additionally, the model included only variables that showed an isolated association with 5% mortality. Other factors that may be associated with the outcomes were not evaluated. The strengths of this study include the use of a representative sample with five years of follow-up and a study city with a low human development index in a developing country. Additionally, identifying risk factors that may be crucial for improving the quality of life and longevity of the population is a significant advantage. Public policies should prioritize promoting regular PA, particularly among older adults, with practices oriented toward health development, physical, and functional independence. These policies should also aim to reduce drug consumption while consistently seeking to improve the quality of life and foster successful aging.

CONCLUSION

Among the older adults included in this study, the determinants of mortality risk were the total number of people living in the same household and the total number of prescribed drugs. These findings suggest that drug prescriptions should be approached with caution in this population. Furthermore, promotion of healthier lifestyles and greater independence in daily activities should be prioritized. Conversely, greater hip circumference and increased PA were also inversely associated with mortality, suggesting that improving these factors could help reduce the risk of mortality. Regular screening of older adults is essential for monitoring their overall health status, identifying potential health issues early, and enabling timely and appropriate interventions. Such interventions can improve the quality of life and contribute to healthy aging.

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Burnout and resilience among intensive care workers facing the end of the COVID-19 pandemic: a cross-sectional study

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ABSTRACT

BACKGROUND: Burnout is a global problem, and resilience may support the well-being of healthcare workers (HCWs) in stressful conditions.

OBJECTIVES: This study aimed to evaluate the association between burnout and resilience among HCWs in intensive care units (ICU) during the coronavirus disease 2019 (COVID-19) pandemic.

DESIGN AND SETTING: A cross-sectional study was conducted in the ICU of four public hospitals in Fortaleza, Brazil.

METHODS: A face-to-face survey was conducted among HCWs in the ICUs of four public hospitals in Fortaleza between January and August 2023. The participants completed questionnaires on burnout and resilience.

RESULTS: A total of 194 professionals, including physichians (24%), nurses (29%), nursing technicians (25%), and physiotherapists (22%), completed questionnaires on burnout and resilience through face-to-face interviews. Most professionals (62%) presented with overall burnout symptoms, and an inverse association was observed between resilience and burnout. However, 16 of the 44 (34%) HCWs with the highest resilience scores experienced burnout. Furthermore, younger age and higher workload were associated with a higher prevalence of burnout.

CONCLUSION: Determinants of burnout were identified among ICU staff members during the last year of the COVID-19 pandemic. Resilience helped HCWs cope with burnout. However, some of the most resilient HCWs presented with high levels of burnout. Efforts are necessary to implement resilience-building tools, yet public health policies to improve ICU organizational issues are more important and urgent for promoting sustainable well-being among professionals, particularly during challenges such as pandemics. Introducing resilience-building tools and implementing public health policies are necessary to improve ICU management and promote sustainable well-being among healthcare workers in high workload settings.

INTRODUCTION

The escalating demands placed on healthcare systems during the coronavirus disease 2019 (COVID-19) pandemic have severely strained intensive care unit (ICU) healthcare workers (HCWs), especially younger professionals, those with less experience, and those with increased workloads.[1–3] The global burnout epidemic has affected thousands of health professionals and has become a public health problem. In the face of this global pandemic, the World Health Organization recognized burnout as an occupational illness and incorporated it into the International Classification of diseases (ICD-11).[4]

The inverse association between burnout and resilience was well documented in a national survey of healthcare professionals conducted prior to the pandemic.[5] Another large-scale survey of ICU HCWs in 2021 demonstrated that higher levels of resilience were associated with reduced symptoms of anxiety, depression, and post-traumatic stress disorder.[6] However, there is a scarcity of studies investigating the levels of burnout and association with resilience among ICU HCWs toward the end of the COVID-19 pandemic.[7]

METHODS

Study Design, setting, and participants

This survey was conducted in public adult ICUs in four tertiary hospitals in Fortaleza, Brazil, from January to August 2023. All HCWs, including physicians, nurses, nurse technicians, and

physiotherapists signed a written consent form and answered questionnaires on burnout and resilience through face-to-face interviews. This study was approved by the National Research Ethics Committee (Protocol No. 04582818.6.00005054/2019).

Questionnaires

The Resilience Scale for Adults (RSA)[8,9] is organized into six factors, and the scores are calculated using total values ranging from 33 to 231, with higher scores indicating higher levels of resilience.

The Maslach Burnout Inventory (MBI) contains three domains of burnout: emotional exhaustion, depersonalization, and professional efficacy. Consistent with the convention, we considered HCWs with a high score on the emotional exhaustion subscale (scores ≥ 26 on a 0–54 scale) and/or depersonalization subscale (scores ≥ 9 on a 0–30 scale) of the MBI to have at least one manifestation of professional burnout.[5,10]

Statistics

A previous study showed mean (SD) resilience of 178.17 ± 22.44 among HCWs.[11] The z-score (z) was 1.96, the margin of error (e) was 0.05, and, assuming a similar mean with a 95% confidence interval (CI), 160 participants were required.

Standard descriptive statistics were used to describe healthcare worker characteristics, a chi-square test was used to compare resilience and burnout, and multivariable logistic regression was used to examine the association between resilience and burnout, adjusting for sex, age, occupation, weekly working hours, and employment at two or more hospitals. Independent variables were selected from the literature. Multicollinearity was assessed using the variance inflation factor (VIF) and values > 2 were excluded. All tests were two-sided with type I error rates of 0.05. All analyses were performed using IBM SPSS Statistics for Windows, version 26.0.

RESULTS

In total, 194 HCWs participated in this cross-sectional study, including 46 physicians (24%), 56 nurses (29%), 49 nursing technicians (25%), and 43 physiotherapists (22%). Most patients were female (71%), and 50% were under 35 years of age. A total of 62% of the participants presented high levels of global burnout. Importantly, none of the respondents felt supported by their healthcare institution.

The mean (SD) resilience total score was 176.3 ± 28.2 and the median (Interquartile range 25%–75%) was 181(155-199) out of 231 scores. A total of 76% of HCWs with the 25th resilience score had burnout symptoms, and 34% of HCWs with the 75th resilience score had burnout symptoms (**Table 1**).

Multiple variable analysis revealed an inverse association between resilience and burnout. Each 1-point increase in resilience score was associated with lower odds of emotional exhaustion, depersonalization, and overall burnout symptoms [odds ratio (OR) 0.97; 95% CI (0.96–0.99), OR 0.97; 95% CI (0.96–0.99), and OR 0.97; 95% CI 0.96–0.98), respectively]. Working in more than two hospitals increased the odds of emotional exhaustion, depersonalization, and overall burnout symptoms [OR 2.48; 95% CI (1.20–5.11), OR 2.71; 95% CI (1.23–5.94), and OR 3.03; 95% CI (1.40–6.75), respectively]. HCW younger than 35 years of age had higher odds of emotional exhaustion and overall burnout symptoms [OR 2.25; 95% CI (1.06–4.77) and OR 3.32; 95% CI (1.12–4.82), respectively] (**Table 2**).

Table 1. Emotional exhaustion, depersonalization, and overall burnout proportions across percentiles of resilience scores among healthcare workers

Variables	25th (≤ 154 points) (n = 47)	25th–75th (155–199 points) n = 100	75th (≥ 200 points) n = 44
Overall Burnout*	36 (76%)[#]	68 (68%)[†]	16 (34%)
Exhaustion*	33 (70%)[§]	58 (58%)[†]	14 (31%)
Depersonalization*	29 (61.7%)[a,b]	36 (36%)[c]	7 (15.9%)

* Chi-square test and post hoc analysis for pairwise comparisons. [#] 25th versus 75th (P < 0.05); [†] 25th–75th versus 75th (P < 0.05); [§] 25th versus 75th (0 < 0.05). [†] 25th–75th versus 75th (P < 0.05); [a]25th versus 25th–75th (P < 0.05); [b] 25th versus 75th (P < 0.05); [c]25th–75th versus 75th (P < 0.05).

DISCUSSION

This cross-sectional study demonstrated that HCWs in the ICUs of public hospitals remained vulnerable to burnout at the end of the COVID-19 pandemic. An association between higher resilience and less burnout symptoms was identified; however, some of the most resilient professionals did experience burnout. Other conditions such as increased workload and younger age were associated with a higher prevalence of burnout. Despite the high levels of burnout, healthcare professionals do not receive support from healthcare institutions. This highlights the need to invest in institutional policies to mitigate this problem.

The proportion of respondents with global burnout in a previous multicenter study,[3] was closer to ours (51% versus 62%). In 2020, a survey conducted by our group in the same ICUs showed a similar prevalence of emotional exhaustion and depersonalization compared to data from 2023 (48% versus 54% and 29% versus 37%, respectively). This finding indicates that the HCWs continued to work under stressful conditions.

The association between workload, younger age, and burnout has been demonstrated by other studies.[1,12] Employment at more than two hospitals is a modifiable factor that hospital managers should pay attention to. For example, job stability, good working conditions, and mental health support can help maintain a permanent professional workforce in hospitals.

Younger HCWs showed higher levels of burnout, and there was an imbalance between expectations and the reality of high-demand

Table 2. Multivariable logistic regression model of the association between resilience score and burnout symptoms among 194 healthcare workers

Variables	Characteristics n = 194	High EE Unadjusted OR (95% CI)	High EE Adjusted OR (95% CI)	High DE Unadjusted OR (95% CI)	High DE Adjusted OR (95% CI)	High overall burnout Unadjusted OR (95% CI)	High overall burnout Adjusted OR (95% CI)
Gender							
Female	138 (71%)	reference	reference	reference	reference	reference	reference
Male	56 (29%)	0.58 (0.30–1.11)	0.97 (0.43–2.26)	0.36 (0.19–0.69)	0.97 (0.21–1.14)	1.71 (0.87–3.36)	1.06 (0.46–2.53)
Age in years							
> 35	97 (50%)	reference	reference	reference	reference	reference	reference
≤ 35	97 (50%)	1.58 (0.89-2.81)	**2.25 (1.06–4.77)**	**2.16 (1.19–3.90)**	2.04 (0.93–4.50)	**2.14 (1.17–3.92)**	**3.32 (1.12–4.82)**
Working in more than two hospitals	83 (42.8%)	**2.40 (1.33–4.34)**	**2.48 (1.20–5.11)**	**2.45 (1.35–4.46)**	**2.71 (1.23–5.94)**	**2.87 (1.53–5.38)**	**3.03 (1.40–6.75)**
Working More than 40 hours per week	188 (96%)	1.83 (0.95–3.47)	1.13 (0.67–0.99)	0.77 (0.39–1.52)	0.77 (0.33–1.77)	2.12 (1.10–4.07)	1.63 (0.74–3.59)
Profession							
Physician	46 (23.7%)	reference	reference	reference	reference	reference	reference
PT	43 (22%)	**0.38 (0.16–0.90)**	0.53 (0.21–1.71)	**0.22 (0.08–0.59)**	0.48 (0.15–1.61)	**0.27 (0.11–0.68)**	0.43 (0.15–1.41)
Nurse	56 (28.8)	1.05 (0.46–2.37)	1.46 (0.46–3.42)	1.15 (0.52–2.51)	2.21 (0.75 6.29)	1.05 (0.43–2.58)	1.82 (0.59–5.65)
Nurse technicians	49 (25.2%)	0.51 (0.22–1.17)	1.06 (0.36–2.91)	**0.32 (0.13–0.77)**	0.50 (0.21–1.86)	**0.39 (0.16–0.94)**	0.93 (0.32–2.72)
Resilience scores (mean ± SD)	176.3 ± 28.2	**0.97 (0.96–0.98)**	**0.97 (0.96–0.99)**	**0.97 (0.96–0.98)**	**0.97 (0.96–0.99)**	**0.97 (0.96–0.98)**	**0.97 (0.96–0.98)**

Abbreviations: EE = emotional exhaustion; DE = depersonalization; OR = odds ratio; CI = confidence interval; PT = physiotherapist; SD = standard deviation.

tasks in ICUs for this group of professionals. Encouraging partnerships between more experienced and younger healthcare professionals can help them.

Despite the small sample size, this study found an inverse relationship between burnout and resilience.

CONCLUSION

This cross-sectional study of four public hospitals suggests that HCWs remain vulnerable to burnout even toward the end of the COVID-19 pandemic. This study also supports the clinical relevance of the identified modifiable factors of burnout that should be considered to mitigate stress in HCWs. Although resilience protects against burnout, some of the most resilient professionals presented burnout, suggesting that efforts to strengthen resilience are important. However, broader ICU system-level improvements are needed to promote sustainable well-being among healthcare workers, particularly during pandemics.

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Autism Spectrum Disorder in adults: an integrative review about strategies for promotion and maintenance of quality of life

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Mental health.

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Adults.

ABSTRACT

BACKGROUND: People with Autism Spectrum Disorder (ASD) experience phases of life beyond childhood, which increase the difficulties inherent in each cycle. In contrast, the scientific literature lacks broad reviews of developmental strategies regarding quality of life, even though ASD encompasses changes in social, communicative, and behavioral skills.

OBJECTIVE: This study aimed to identify strategies for promoting and maintaining quality of life among adults diagnosed with autism.

DESIGN AND SETTING: This integrative review was conducted in Brazil.

METHODS: This review searched the Scopus and Web of Science databases, from strategies that combined the descriptors ("Autism Spectrum Disorder"), ("Autism"), ("Aging"), and ("Quality of life"). Original studies with the full text available in English published between 2018 and 2023 were included, if they responded to the eligibility criteria.

RESULTS: In total, 3,098 studies were identified, of which 44 were selected to compose the bibliographic sample of this review. The population sample included 184,653 participants diagnosed with ASD, aged on average 43.5 years old. The following were described for adults with autism: 1) cognitive aspects, 2) aspects related to suffering/mental illness, and 3) strategies to promote quality of life.

CONCLUSION: This research contributes to basic clinical practice and promotes responsible care that attends to the health needs of people with autism throughout life. Early interventions in autistic adults and the availability of support throughout life are essential for maintaining cognitive health and quality of life.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder involving changes in social, communicative and behavioral skills. Diagnosis is supported by stereotypical and repetitive behaviors (e.g., *flapping*), restricted interests, difficulty interpreting social scenarios, reduced peer interactions, diminished shared emotions, limited visual contact and vocal variation, rigidity with rules, resistance to change, and preference for objects due to texture or smell.[1]

Its prevalence ranges from 1% to 2% of the global population, with rates increasing in recent research.[1] Since Kanner conducted the first study with children diagnosed with autistic affective contact disorder, this neurodevelopmental disorder has been read as a childhood disorder, with literature on this disorder in adolescents, adults and elderly adults being scarce.[1–4] Despite early conceptions of autism as a childhood disorder, projections estimate 1,7 million autistic individuals over age 65 in the United Kingdom by 2030,[5] and 50 thousand autistic people enter adulthood annually in the United States.[6] This underscores the necessity of research addressing autism across all life stages to inform clinical care.

Although some reviews focus on transitions to adulthood or psychosocial aspects of aging in ASD, studies exploring the condition in later life remain scarce.[7,8] Approximately 70% of individuals with autism have at least one comorbid mental disorder, such as anxiety, depression, or structural language disorders, and 40% have two or more comorbidities.[2] Medical conditions such as epilepsy, sleep disorders, and constipation further increase health risks, emphasizing the importance of strategies to enhance quality of life in this population.[1,2]

By 2023, only 2% of ASD studies had addressed adults and elderly people,[9] limiting evidence-based strategies for these groups. Analysis of the repercussions of the pandemic on neurodivergent children's lives, reveal negative aspects, such as behavioral changes, mood, hyperactivity and communication;[10–12] on other age groups are important for a broader understanding of these impacts. Additionally, low-income countries, including Brazil, often lack basic autism statistics, where data on aging in ASD are minimal.[11,13] This hinders the planning of care for adults and elderly adults with ASD and limits research outcomes.

In line with the association of ASD with multiple comorbidities, the increase in this population beyond childhood and its greater vulnerability, as well as the lack of broad reviews regarding paths to healthy development, justify and reiterate the need for this review. Therefore, this article aimed to complement the scientific literature on this subject by proposing and identifying strategies for promoting and maintaining quality of life among adults diagnosed with autism to support adequate care for the characteristics of this population.

METHODS

This integrative review aimed to promote a synthesis of knowledge on the issue: "What strategies can be adopted to improve and maintain the quality of life of people with autism after childhood?" The research was conducted in six stages: 1) elaboration of the guiding question; 2) literature search; 3) data collection; 4) critical analysis of the included studies; 5) discussion of the results; and 6) presentation of a review integrative.[14]

The Health Sciences Descriptors (DeCS) used—("Autism Spectrum Disorder"), ("Autism"), ("Aging") It is ("Quality of Life")—were combined with the Boolean operator AND and applied in the following strategies of searches: 1) ("Autism Spectrum Disorder") AND ("Aging"); 2) ("Autism") AND ("Aging"); 3) ("Autism Spectrum Disorder") AND ("Aging") AND ("Quality of life"); 4) ("Autism") AND ("Aging") AND ("Quality of life"). This research was conducted in August 2023 using the Scopus and Web of Science databases.

Original studies with full text available in English, published in the last five years (2018–2023) that responded partially or fully to the research question were included as eligibility criteria. A study partially answered the research question when it did not directly present strategies to improve quality of life but contributed to the understanding of the experience of ASD in adult life by discussing neurocognitive aspects and/or aspects related to suffering or mental illness. Duplicate articles were excluded if in another language; other textual genres, such as letters, comments, reports, summaries, and editorials; incomplete articles, such as protocols; reviews of any type; articles unavailable, considering a failed access attempt via the institution and a request to authors not responded to; in addition to studies not related to the objective of the research, that is, whose population was 1) people under 18 years of age and/or 2) people without a formal diagnosis of ASD, such as people with an extended phenotype and/or family members/caregivers; and/or 3) those that did not address issues related to growth, aging, and/or quality of life of adults with ASD.

Initially, studies were screened by reading the titles and abstracts, with the help of software Rayan,[15] followed by reading the eligible articles in full. This stage was performed by two independent, blinded reviewers (GGCL and FBMM). The selected studies were systematized in a database using Microsoft Excel®, considering the following variables: authors, year of publication, study location, study design, sample (number of participants, age range and gender ratio when informed), main results, strategies to promote quality of life in adults with ASD, and limitations of the study.

Systematization involved the stages of identification, registration, analysis, and interpretation of the selected studies. Numerical data are presented based on the main results and strategies to promote quality of life in adults with ASD. Descriptive statistics, in absolute numbers and percentages, and qualitative data were categorized considering 1) cognitive aspects, 2) suffering/mental illness, and 3) strategies to promote quality of life.

RESULTS

In total, 3.098 studies were published between 2018 and 2023 (Scopus = 1.476, Web of Science = 1,622), of which 44 were selected to compose the bibliographic sample of this review according to the inclusion and exclusion criteria. **Figure 1** illustrates this process.

Characterization of studies

The sample of 44 articles was composed of 651.738 participants, of whom 184,653 (28.33%) were diagnosed with ASD, with ages ranging from 18 to 92 years, with an average age of 43.5 years. Among the selected articles, 95,4% were mixed, comprising men and women, and one article was composed exclusively of men and two exclusively of women.

All analyzed articles were conducted in developed countries: the United States (50%), the Netherlands (13.63%), the United Kingdom (11.36%), France (6.81%), Australia (6.81%), Germany (4.54%), South Korea (2,27%), Canada (2,27%), England (2,27%), and countries of Europe unspecified (2,27%). The study designs were mainly observational (95.45%), with only two being interventional. The individual characteristics of the studies are summarized in **Table 1**.

Eight articles (17.02%) included people with ASD associated with psychiatric comorbidities, such as intellectual development disorder (2.13%), anxiety and depression (6.38%), depression (2.13%), and others, such as attention deficit hyperactivity

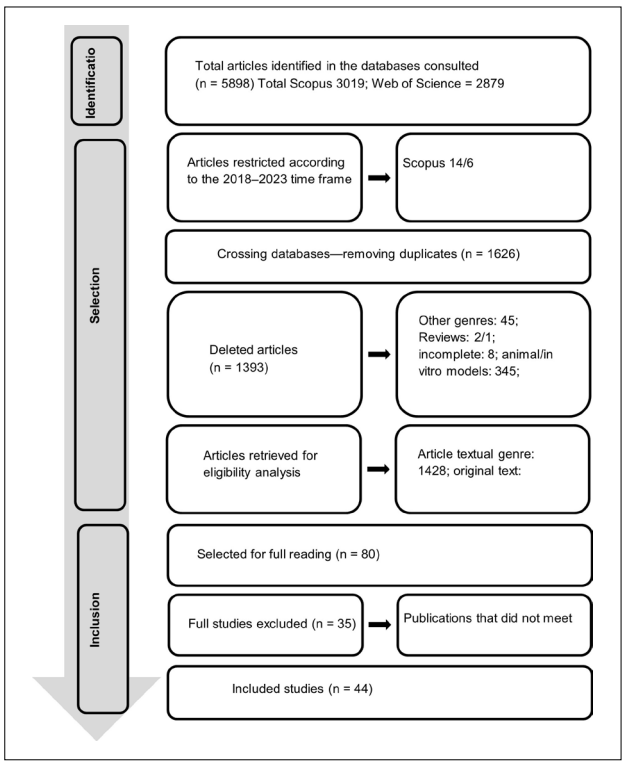

Figure 1. Flow chart bibliographic selection.

disorder (ADHD), obsessive compulsive disorder (OCD), and schizophrenia (2.13%).

The analyzed articles considered a diversity of approaches to diagnosis/confirmation of diagnosis of ASD: 1) standardized instruments, such as the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R), providing structured and objective assessments of ASD symptoms;[16,17] 2) formal clinical assessment conducted by mental health professionals for direct observation of individuals' behavior;[18] 3) use of established diagnostic criteria, such as those from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Classification of Diseases (ICD-10), in different contexts to identify ASD;[19,20] 4) combined analysis by multidisciplinary teams of specialists, conducting formal clinical diagnoses before inclusion and confirming the diagnosis with instruments such as the ADOS-2 and Autism Spectrum Quotient (AQ);[21] 5) analysis of electronic health records extracted from medical institutions, providing additional information for diagnosis confirmation.[22,23] The importance of confirming the diagnosis of ASD based on standardized instruments, such as those mentioned above, was also highlighted.[24]

Cognitive aspects

The microstructural integrity of the left dorsal premotor tract and supplementary motor area is directly associated with the severity of restrictive behaviors in adults with ASD.[35] However, these adults demonstrated comparable performance to controls on skills such as verbal comprehension and perceptual reasoning. However, they face challenges, including reduced processing speed and difficulties in working and visual memory tasks.[54]

Additionally, adults with ASD face difficulties in a range of areas, from empathy to sensory sensitivities and motor skills, highlighting the importance of ongoing support throughout life.[59] One of the main findings was the variation in cognitive performance. While adults with autism demonstrated no significant differences from their neurotypical peers in domains such as fluency, theory of mind, response speed, or verbal memory, a decline in long-term visual memory was observed.[51] This finding highlights the importance of early detection and targeted interventions to maintain cognitive health over time.

Paradoxically, age appears to exert a possible protective effect on the theory of mind in people with ASD, yet older adults with ASD face higher levels of personal distress in tense social environments.[59] The relationship between aging and ASD is also evident in the reduction of brain connectivity, highlighting the importance of considering other factors that interfere with neurobiological aspects when planning interventions and support for adults with ASD.[21,56]

Decreased mental flexibility in adults with ASD is associated with repetitive behaviors and variations in learning. The majority do not meet the criteria for "successful aging" because they present greater number of medical comorbidities and difficulties in accessing care—this aspect interferes with and implies greater difficulty in establishing and maintaining social relationships in everyday life.[36]

Motor aspects are also affected, with deficits in manual dexterity, coordination, and strength, in addition to reduced functional connectivity between sensorimotor regions. The identification of these aspects indicates the potential for preventing accelerated functional decline through greater commitment, intervention with greater monitoring, and corroborating a better quality of life.[40]

Although no significant differences in age, gender and Intelligence Quotient (IQ), adults with ASD exhibit a higher incidence of alexithymia are presented, they have greater difficulty recognizing and expressing emotions.[59] Middle-aged men with ASD have higher scores on social cognition, while it was identified in studies that elderly adults with ASD face a higher incidence of epilepsy, but a lower incidence of depression and anxiety.[56]

Adults diagnosed late with ASD show differential cognitive skill performance. Therefore, measures that improve executive function, such as practicing adequate physical activities and specialized medical monitoring, considering the individuality of each subject, are important to improve the quality of senescence for people with ASD.[19]

Table 1. Individual characterization of studies

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Abbott, Happé and Charlton (2018)[19]	Cross-sectional study (UK)	134 participants diagnosed with ASD (97 men and 37 women). Age range: 18–75 years old. Average age: 31.14.	Adults diagnosed late with ASD showed better performance in certain cognitive skills, such as speed and sequencing than in typical age norms, while other executive skills followed normal aging patterns.	Include therapies that aim to improve executive functions, adequate physical activity, and specialized medical monitoring. Additionally, considering group activities, social practices, and interventions specific to comorbidities may be beneficial. However, approaches should essentially be personalized based on individual needs, such as promoting autonomy and reducing anxiety.
Abigail Dickinson et al. (2022)[25]	Cross-sectional study (USA)	180 participants (93 diagnosed with ASD and 87 controls without diagnoses of ASD). Age range: 18–70 years old.	Neurophysiological aging was shown to be accelerated in adults with ASD, compared to adults without ASD. However, nonverbal cognitive abilities in both groups are similar, which suggests that oscillatory characteristics associated with cognitive processing may vary.	Not described.
Baxter et al. (2019)[16]	Cross-sectional study (USA)	76 sex participants masculine(42 diagnosed with ASD and 34 controls with diagnosis of ASD). Age range: 18–60 years old.	The groups did not differ on estimated IQ and performance of fluency. Young and elderly adults with ASD showed poor performance on cognitive tests. Large age-related reductions in subcortical structures focusing on the left thalamus were observed in the study, which suggests possible weakening in frontal-subcortical connectivity in older adults or differences in processing internally directed task demands.	Using fluency networks helps us form an even clearer picture of how language is altered by aging. By a better understanding of the brain networks involved in producing similar levels of cognitive performance, it may also have implications for the ways in which these compensatory mechanisms may be involved in other cognitive areas.
Bathelt et al. (2020)[21]	Cross-sectional study (Netherlands)	51 participants diagnosed with ASD (68.6% men and 31.4% women). Age range: 30–74 years old. Average age of 45 years.	Aging has been shown to affect brain connectivity, especially reducing Default Mode connections. This indicates that aging and ASD affect the brain in specific ways.	Not described.
Bernhardt et al. (2020)[26]	Interventional study (USA)	5 participants diagnosed with ASD (3 men and 2 women). Age range: 20–25 years old.	A program was developed in which participants stayed in student residences, participating in activities: 1) in the house: house rules, safety plans, hygiene routines, household chores, meal preparation; and 2) on campus: participation in career development, credit and finance, first aid safety, arts, and local community workshops, with varying levels of support depending on the person, activity, and environment. The intervention proved to be effective, participants demonstrated the quality learning of life in all constructs of active engagements and expression of interest in future life projection.	Join some type of community where they can have support in reaching their own wellness goals.
Bishop-Fitzpatrick e Rubenstein (2019)[23]	Observational study (USA)	143 participants diagnosed with ASD. Age range: 40–88 years old.	Physical and mental health conditions such as immunological (70.6%), cardiovascular (49%), sleep disorders (85.3%), gastrointestinal (49.7%), neurological (55.9%) and psychiatric (72%) disorders were prevalent. Middle-aged and older adults with ASD and intellectual disability had higher prevalence of epilepsy and less of depression/anxiety compared to those without intellectual disabilities.	It highlights the importance of health professionals, especially those working in family health, internal medicine, and geriatrics, being aware of the multiple health conditions that can affect adults with ASD. This suggests the need for additional training for these professionals in treating chronic conditions associated with ASD.

Continue...

Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Braden et al. (2022)[27]	Cross-sectional study (USA)	133 participants (67 diagnosed with ASD and 66 controls with no diagnosis of ASD). Age range: 18–71 years old.	A mindfulness-based intervention proved to be beneficial in improving quality of life related to psychological health and reducing difficulties related to disability in adults with ASD.	Support/education and stress reduction interventions based on mindfulness improve quality of life related to mental health, being more effective for women with ASD. Focusing on emotional awareness and attitudes of acceptance can be crucial to improving the quality of life of this population.
Bush et al. (2018)[28]	Cross-sectional study (Canada)	496 participants (248 diagnosed with ASD and 248 controls which diagnosis of ASD; all female participants). Age range: 18–30 years	Participants with ASD reported significantly lower sexual desire compared to participants without ASD, and less involvement in sexual behaviors throughout their lives, which included a significant reduction in the number of reported sexual activities. Sexual satisfaction does not differ significantly between the two sample groups. Notably, both had high rates of nonbinary or fluid gender identities, as well as a variety of sexual orientations.	Not described.
Chan et al. (2018)[2]	Longitudinal study section (USA)	406 participants (adolescents and adults diagnosed with ASD, 72.4% men). Age range: ≥ 18 years.	The most powerful predictors of whether a person with ASD and DID will remain in employment were living in an area with a larger population, having access to inclusive education as a child, and having more independent daily living skills. Family factors were also predictive, such as higher income and more extensive maternal social connections.	Individuals with ASD and DID deserve special attention in intervention and professional training programs related to daily living skills, prioritizing the teaching of self-care skills, training in domestic skills, and exposure to an inclusive lifelong learning environment.
Chan et al. (2023)[29]	Longitudinal study (USA)	40 Participantsdiagnosed with ASD (27 males and 13 females). Age range:≥ 18 years. Average age of 37 years.	Many adults with autism was shown to want social connections. The study provides initial support about the context where people with ASD seek to develop social interactions, namely: vocational contexts, neighborhoods, common interest groups, support services and inclusive environments, and networks and applications online.	Establishing in-person support groups with other adults with ASD who have common interests, for example: game nights, participation in religious communities, work, volunteering, online community participation specific to this population or creating an autism task force focused on supporting co-workers who are also on the spectrum.
Charlton et al. (2023)[30]	Cross-sectional study (USA)	388 participants diagnosed with ASD. Age range: 40–83 years.	Evidently, the subjective social support was positively associated with quality of life in older adults with autism. Symptoms of depression and anxiety had a negative impact on quality of life. Additionally, age positively affected the psychological and environmental quality of life, while sex assigned at birth influenced physical and environmental quality of life.	Positive social support impacts the quality of life in elderly and young adults with ASD. Subjective social support plays a significant role in all aspects of quality of life, while social interactions and instrumental support contribute to specific domains. Social support is crucial to quality of life in older adults with autism, considering demographic factors and depression.
Clark et al. (2023)[31]	Longitudinal study (USA)	151 participants diagnosed with ASD. Age range: 18–28 years old.	Notably, some particularities of the public with ASD that can influence their quality of life and professional stability: 1) importance of early interventions; 2) diversity in trajectories; and 3) access to services, that is, offering employment support.	Professional activities such as employment and postsecondary education increase subjective well-being in adults with ASD. Participants involved in independent vocational activities had higher ratings of well-being and a greater propensity for social contacts, highlighting the importance of these activities.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Crawley et al. (2020)[24]	Observational study (Europe)	321 participants diagnosed with ASD. Average age: 18–30 years.	The study revealed that adults with ASD show decreased mental flexibility, which is linked to repetitive behaviors and differences in the way they learn.	Understanding differences in behavior can guide personalized interventions, considering individual preferences, sensitivities, and learning patterns. Understanding how the learning environment influences performance can lead to more adapted and effective therapeutic approaches.
DaWalt et al. (2021)[22]	Observational study (USA)	2,187 participants diagnosed with ASD (78.54% men). Average age: 30.6 years.	The results suggest differences in the prevalence of diseases and use of healthcare related to ASD and gender, with women with ASD presenting greater risk and greater use of healthcare in various conditions. However, specific details about the medical conditions and use of health services related to ASD and gender are not described.	It suggests the intensification of the use of healthcare by women with ASD, considering biological differences, diagnostic processes, perceptions, and responses from society. Findings emphasize the importance of examining healthcare utilization alongside prevalence, highlighting the specific challenges faced by women with ASD, and advocating for personalized interventions and supports.
Gabbai and Garreau (2022)[32]	Cross-sectional study (France)	135 participants diagnosed with ASD (61.5% men and 38.5% women). Age range: 18–92 years old. Average age: 53 years old, with the majority of participants between 35 and 74 years old (85%).	The study highlights that in adulthood, the emphasis is on associated disorders and psychiatric comorbidities, instead of the fundamental characteristics for the diagnosis of ASD. It is important to adopt a functional approach that reveals the underlying psychological distress and the coping strategies developed by patients.	The relevance of clinically addressing associated disorders and psychiatric comorbidities, prioritizing a functional perspective that reveals patients' adaptation to psychological distress. It concludes by highlighting the need for structured institutional work to deal with the diversity of these patients and ensure coherent approaches.
Geurts et al. (2020)[20]	Observational study (Netherlands)	101 participants diagnosed of ASD (all men and elderly adults). Average age: 60–85 years.	The results suggest that older men with autism diagnosed with ASD may report more challenges in cognitive flexibility, planning, processing speed, and working memory in daily life, although they do not show significant differences in performance on neuropsychological tests compared to older adults without ASD.	Strategies to improve the quality of life of these autistic adults may include interventions based on an understanding of these daily challenges, possibly involving training in internal or external strategies. Understanding the specific causes of these difficulties can guide personalized support.
Groenman et al. (2021)[33]	Longitudinal study (Netherlands)	135 female participants (58 diagnosed with ASD and 77 diagnosis with ASD). Age range: 31–73 years.	They were not identified statistically significant differences of the suffering of autistic women in relation to the disorder premenstrual dysfunction compared to non-autistic women. Autistic women presented higher psychological and somatic complaints, mainly ASD, also presenting complaints of ADHD, without an increase in urogenital complaints.	More substantial social support during stressful events, greater physical fitness, better coping strategies, and better sleep quality. Future studies are needed to analyze the link between menopausal complaints and estrogen levels, and the sensitivity to them shown by women with autism.
Hand et al. (2019)[34]	Case-control study (USA)	21,792 participants diagnosed with ASD. Age range: 18–59 years old.	Adults with autism were 4.3% in the study who had at least one medical encounter related to suicidal ideation, which is similar to estimated prevalence rates for the general population (3%-4%). However, 4.1% of adults with autism had at least one medical encounter related to suicide attempts or self-harm, which is significantly higher than the general population (0.4%-0.6%). Linked to this, risk factors such as bipolar and unipolar depression were strongly associated with suicidal ideation in people with ASD.	Adults with ASD and co-occurring intellectual disability had significantly lower odds of a medical encounter for suicidal ideation, but significantly higher odds of attempted suicide/self-inflicted injury.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Hau et al. (2021)[35]	Cross-sectional study (USA)	52 participants (28 diagnosed with ASD, 22 men and 6 women; and 26 controls without a diagnosis of ASD, 8 being men and 18 women). Age range: 40–70 years old.	Reduction in microstructural integrity of the left dorsal premotor tract (PMd) and supplementary motor area in each substrate (SMA-cst) was associated with greater severity of restrictive behavior in adulthood.	This finding may reflect a greater ability to appropriately select actions based on associated stimuli and inhibit behaviors, such as stereotypies, in individuals with more effective secondary motor relays.
Hwang, Foley e Trollor (2018)[36]	Cross-sectional study (Australia)	92 participants diagnosed with ASD. Age:≥ 40 years.	Evidently, the majority of adults with ASD do not meet the criteria for "successful aging" as defined by the Rowe and Kahn model, with difficulties in maintaining social relationships and engaging in activities of daily life, resulting in less social participation.	Notably, adults with autism face additional challenges, such as a greater number of medical comorbidities and difficulties accessing medical care, which requires greater attention to these specific demands. The need for strategies to promote social inclusion throughout the lives of these individuals is also highlighted.
Janice Hau et al. (2022)[37]	Cross-sectional study (USA)	73 participants (35 diagnosed with ASD and 37 controls which diagnosis of ASD). Age range: 41–70 years.	People with ASD have been shown to have a stronger connection between structural and functional brain connectivity, especially in the right hemisphere. Differences in the structure and connectivity of cerebral white matter exist in adults with ASD compared to neurotypical adults. However, these characteristics may vary depending on the activity that the adult with ASD is exposed to.	Not described.
Klein et al. (2022)[38]	Cohort study (USA)	210 participants diagnosed with ASD (89 males and 121 females). Average age: 55.63 years.	High rates (30%) of cognitive decline were found in autistic adults, with symptoms such as lack of interest in hobbies and memory problems. And that autistic women may be more vulnerable to decline, highlighting the importance of early screening and appropriate care.	Not described.
Lever e Geurts (2018)[39]	Cross-sectional study (Netherlands)	440 participants (241 with diagnosis of ASD and 199 controls without diagnosis of ASD).	Adults with ASD face difficulties related to empathy and sensory sensitivities throughout their lives, with characteristics more evident in middle age (49 years) and less in young/older adults.	Understanding the variability of differences in ASD characteristics across adulthood across the lifespan can guide personalized support approaches.
Link et al. (2021)[40]	Cross-sectional study (USA)	33 participants diagnosed with ASD. Average age: 40–65 years.	Adults with ASD have deficits in several motor skills, including manual dexterity, coordination, and strength and flexibility, compared to the control group. Furthermore, functional connectivity between sensorimotor regions was reduced in the ASD group, and connectivity patterns were more variable among individuals with ASD than in the control group.	Understanding variations in sensorimotor connectivity highlights the importance of personalized approaches and longitudinal monitoring to better understand changes over time. This may be crucial to develop specific interventions and improve the quality of life of adults with ASD, potentially preventing accelerated functional declines.
Mason et al. (2019)[41]	Cross-sectional study (UK)	69 Participants diagnosed with ASD (48 men and 21 women). Age range: ≥ 55 years.	Quality of life scores in all domains were lower for individuals who reached the points of clinical cutoff indicators for depression according to the Hospital Anxiety and Depression Scale (HADS) (F (8.126) = 6,171, P < 0.001); results were similar for anxiety (F (8.126) = 3,902, P < 0.001) with the exception of the social quality of life domain, where no significant differences were found in the score. Subjective quality of life did not differ according to participation in normative outcomes (F (12.124,64) = 1,363, P = 0,192).	Perceived informal rather than formal support predicted higher subjective quality of life. Religious communities may offer a consistent source of informal support and acceptance. Providing suitable environments for people with ASD is significantly related to subjective and focus on individual provision dualized.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Miot et al. (2019)[42]	Observational study (France)	63 participants diagnosed with ASD (3.7 men for each women). Average age: 43 ± 15.1 years.	The most frequent comorbidities identified were constipation (54%), epilepsy (28.6%), and chronic kidney disease (25.4%). Analyzes associated ASD severity with epilepsy. Comorbidities impacted communication skills and daily living. Comorbidity burden was influenced by age, polypharmacy, and level of autonomy.	Promoting autonomy and personalized assessment can improve the quality of life of adults with ASD and intellectual disabilities. Reducing polypharmacy and considering specific strategies for comorbidities such as constipation are important approaches. Close attention to inflammation and a comprehensive geriatric assessment may also benefit these individuals.
Miot et al. (2022)[43]	Observational study (France)	63 participants diagnosed with ASD (27% women and 73% men). Median age: 46 years old, with 52.38% participants under 50 years old and 47.62% aged 50 years or over.	The results highlight the importance of considering risk management and polypharmacy, mental, and neurological health problems. Prevention and treatment of specific conditions, such as epilepsy, kidney, and cardiovascular problems in elderly adults, are crucial to extending healthy life expectancy. Furthermore, identifying patterns of multimorbidity can provide insights into pathological aging and help personalize healthcare.	This study highlights the importance of ongoing healthcare and early geriatric assessment in people with ASD. Findings indicate potential associations between multimorbidity and the gut-brain axis, emphasizing the need for holistic strategies to improve quality of life.
Mogavero, Hsu (2020)[44]	Cross-sectional study (USA)	134 participants (46 diagnosed with ASD and 88 controls which diagnosis of ASD). Age range: 18–57 years old.	Many participants with ASD did not understand romantic relationships, although they had already shown interest or been in relationships (41.35%). Participants with ASD had lower percentages in the categories on how they learned to start relationships, with significant statistical differences between country (26.2%), colleagues (8.7%), media (30.4%), and social observation (50%). It was evident that thesexual orientations and minority gender identities showed increased prevalence among individuals with ASD.	Establishing sex education programs to reduce sexual anxiety and allow people with ASD to explore their sexuality with general social skills training and sex education. This education should teach courtship/dating behaviors and how to do so safely, especially if they are with potential partners, *online*, and be trained and taught how to recognize when someone is not interested and when someone is feeling bad about courtship.
Oh Mia et al. (2021)[18]	Intervention study (South Korea)	37 participants diagnosed with ASD (19 from the treatment group and 18 from the delayed treatment group). Average age: 23.5 years.	The Program for the Education and Enrichment of Relational Skills for Young Adults is an evidence-based intervention considered effective in improving relational skills in young adults with ASD. Implemented in young adults with ASD in South Korea, aiming to improve social and relational skills, it demonstrated effectiveness with a high completion rate of treatment (83.78%). After 4 months of participation, significant improvements were observed in the social skills, behavior and mental health of participants with ASD.	It highlights the reduction in symptoms of anxiety and depression, which resulted in significant improvements in the knowledge of social skills, involving the participation of parents as social coaches, with an emphasis on continuous practice. It is suggested that a comprehensive approach can positively influence the quality of life of these adults with ASD.
Pagni et al. (2020)[45]	Cross-sectional study (USA)	177 participants (95 diagnosed with ASD and 82 controls without diagnosed with ASD). Average age: 18–71 years.	Evidently, no significant differences were found between ASD and non-ASD groups in age, gender, and IQ. However, the participants without ASD had a statistically superior performance on the task compared to those with ASD; gender did not influence significantly.	It highlights the importance of understanding these variations in aging trajectories. This may be relevant for the development of specific and personalized therapies. The research highlights the need for future investigations into the underlying neural circuits and how these may influence aging trajectories, providing valuable insights to improve the quality of life of these adults with ASD.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Radhoe et al. (2023)[46]	Cross-sectional study (Netherlands)	720 participants (114 with diagnosis of ASD and 58 without diagnosed with ASD, in addition to a replication group with 261 with diagnosis of ASD and 287 controls without diagnosis ASD). Range age: 30–89 years old.	Based on variables related to aging and autism, of adults with autism, one of these research subgroups demonstrated greater vulnerability with more cognitive and psychological difficulties and lower quality of life. This finding suggests the need for specialized support and care for this specific group of adults with autism.	Not included.
Rocha et al. (2022)[47]	Cross-sectional observational study (USA)	108 participants (54 diagnosed with ASD; 54 controls no diagnosis of ASD). Age range: 18–58 years old.	Evidently, individuals with ASD may face specific challenges in the development of their sexuality, including a self-concept of less positive sex compared to individuals without ASD. Furthermore, a survey highlights the importance of adapting sexual education to meet the needs of people with ASD and highlights the need to better understand how sexual knowledge is related to sexual self-concept in this population.	A need arises for a model of psychosexual well-being that addresses the development of sexuality in adults with ASD. This sexually positive model will allow future studies to develop the identified intrapersonal variables for the enhancement of a more in-depth examination of psychosexual well-being, which should assess whether some variables (sexual self-concept, sexual knowledge, and sexual feelings and attitudes) have a stronger influence on the sexual well-being of this population.
Roestorf, Howlin e Dermot (2022)[48]	Longitudinal study (UK)	440 participants (241 with diagnosis of ASD and 199 controls without diagnosis of ASD). Age range: 19–79 years old.	In this study, differences related to age, sex, and self-report versus third-party report in the characteristics of ASD in adults were analyzed. Adults with ASD presented higher scores in ASD characteristics and sensory sensitivity, with significant differences between sexes. Furthermore, discrepancies between self-report and third-party report, highlighting the complexity in understanding the characteristics of adults with ASD.	It highlights the importance of understanding the difficulties associated with aging and ASD. To improve quality of life, interventions focused on mental health, ongoing support and understanding specific factors such as interests and repetitive behaviors can be explored.
Schott et al. (2022)[49]	Retrospective observational cohort study. (USA)	622,468 participants (155,617 diagnosed with ASD and 466,851 controls no diagnosis of ASD). Age range: 18–64 years old.	Evidently, adults with autism were more likely to present psychiatric comorbidities, including depression, bipolar, anxiety, ADHD, OCD, schizophrenia, and other psychoses; however, they were less likely to present alcohol and drug abuse and bipolar disorder. They were also more likely to have physical health conditions such as Parkinson's disease, endocrine disorders, epilepsy, nutritional conditions, and constipation. However, a lower chance exists of having disorders of the peripheral nervous system, paralysis cerebral, osteoarthritis, gout, and stroke, in that order.	Adults with ASD did not have a higher prevalence of some important health problems (e.g., cardiovascular problems, stroke, cancer, cardiovascular diseases), but they did have a higher probability of others (e.g., nutritional problems, epilepsy, central nervous system disorders).
Smith Da Walt et al. (2019)[50]	Longitudinal study (USA)	406 participants (adolescents and adults diagnosed with ASD, 72.4% men). Age range: ≥ 10 years (follow-up for 20 years). Average age: 21.4 years.	The predictors of mortality limited self-sufficiency in activities of daily living and deficiencies in social reciprocity. Approximately 6.4% of the sample died during the follow-up period. The average age at death was 39 years. Causes of death included chronicled conditions (such as cancer and seizures), accidents (such as choking on food and accidental poisoning), and health complications due to medication side effects.	Limited self-sufficiency responds to environmental influences, for example, employed adults with ASD are more likely to improve their skills because of expectations set by work. It is important to provide interventions designed to develop self-sufficiency in daily life for children, adolescents, and adults with ASD.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Torenvliet et al (2023)[51]	Longitudinal study (Netherlands)	240 participants (128 diagnosed with ASD and 112 controls which diagnosis ofASD). Age range: 24–85 years old.	Evidence against accelerated cognitive decline in adults with ASD exist. No significant differences were observed when comparing people with and without ASD in cognitive domains such as fluency, theory of mind, response speed, inhibition, and verbal memory. Learning among people with autism were shown to develop at a similar pace in both groups.	Not described.
Torenvliet et al. (2021)[52]	Longitudinal study (Germany)	176 participants (88 diagnosed with ASD and 88 controls without a diagnosis of ASD). Age range: 30–89 years old.	The group with ASD performed worse in several cognitive areas, including verbal fluency and the theory of the mind; however, performance was similar in visual memory. Furthermore, no age-related differences were shown in cognitive performance between adults with and without ASD.	Not described.
Torenvliet et al. (2023)[53]	Longitudinal study (Germany)	254 participants (86 diagnosed with ASD 93 and 118 controls which diagnosis of ASD). Age range: 20–79 years old.	Comparisons exist between groups with ASD and controls revealed no significant differences in measures of prepotent response inhibition. However, when controlling response speed, adults with autism made more errors than adults without autism. Furthermore, a significant correlation exists between the hyperactivity/impulsivity scale and response variability in the group without autism.	Not described.
Tse et al. (2019)[54]	Cross-sectional study (England)	55 participants (28 diagnosed with ASD and 29 controls without a diagnosis of ASD). Age range:≥ 50 years.	The group with ASD and control group showed similar performance in verbal comprehension and perceptual reasoning; auditory, visual, and immediate and delayed memory, which suggests that having an autism diagnosis does not confer a risk factor for Alzheimer's. People with ASD presented processing speed reduction. It is poorer performance on visual working memory tasks. It is suggested that the processing speed performance is closely related to levels of independence in daily functioning.	It is recommended that more research should be conducted on processing speed, as it is useful in promoting independent living in individuals with ASD. Therefore, with better knowledge of the cognitive functioning of elderly adults with ASD, the development of interventions and services for this population can be facilitated to meet their needs.
Uljarevic et al. (2020)[55]	Longitudinal study (Australia)	255 participants diagnosed with ASD (151 men and 104 women). Age:≥ 15 years. Average age: 43.75.	The study revealed that anxiety and depression are common in autistic adults throughout their lives, regardless of age. Additionally, women, people with more ASD symptoms, and individuals who live alone tend to have higher anxiety and depression scores.	It highlights the urgent need for adequate assessment and interventions throughout the lifespan to improve the quality of life of adults with ASD. However, the study does not detail specific intervention strategies.
Walsh et al. (2020)[56]	Cross-sectional study (USA)	85 participants diagnosed with ASD. Young people with an average age: 21.1 years Middle-aged adults: 53 years old.	Middle-aged men with ASD had higher scores on social cognition and showed reduced functional brain connectivity, especially in older men with ASD. Elderly adults with ASD had a higher incidence of epilepsy, but a lower incidence of depression/anxiety, regardless of intellectual disability.	This study highlights the importance of considering neurobiological factors and age groups when planning interventions and support for adults with ASD. A personalized approach, considering the specific needs of different age groups.

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Table 1. Continuation

Author and year	Study design and location	Sample	Main results	Strategies to promote quality of life in adults with ASD
Walsh et al. (2022)[57]	Longitudinal study (USA)	50 participants (25 diagnosed with ASD and 25 controls no diagnosis ofASD). Age range: 40–70 years old.	A decline in the long-term visual memory of those with ASD, with the exception of short-term, which is unchanged. Furthermore, hippocampal free water at baseline was found to be significantly correlated with long-term visual memory decline in the group with ASD, making this information important for a possible marker to predict age-related memory decline in the group with ASD.	Adults with ASD are at greater risk for accelerated memory decline, particularly long-term memory, as suggested by the higher incidence of early-onset dementia, the development of prognostic biomarkers will be an important development to inform early diagnosis and accurate treatment.
Yarar et al. (2022)[58]	Cross-sectional study (UK)	136 participants (79 diagnosed with ASD and 57 controls without diagnosed with ASD). Age range: 21–71 years Average age = 44.96 years.	Adults with ASD, both young and older, showed symptoms of autism without significant age-related differences. Both groups experienced mental health difficulties, with depression being the most influential factor in quality of life,surpassing IQ and severity of ASD symptoms. Age affected the quality of social life of older adults with autism, but had no impact on the control group.	Not described.
Zivrali Yarar et al. (2021)[59]	Cross-sectional study (UK)	97 participants (58 diagnosed with ASD and 39 controls without diagnosed with ASD). Age range: 18–50 years old.	No statistically significant differences presented at the intellectual level between groups. The group of young persons with ASD performed worse in theory fell: emotional perception, empathy and awareness of their emotions. A possible protective effect of age on theory of mind in people with ASD was identified. Elderly people with ASD showed higher levels of personal distress in tense social environments. The group with ASD showed higher levels of alexithymia when compared to the group of people with typical development.	Not described.
Zheng et al. (2021)[60]	Qualitative study (Australia)	15 participants diagnosed with ASD (53% women, and one nonbinary participant). Age range: 50–73 years old. Average age: 60.1 years.	Older adults with autism prefer everyday assistive technologies to manage the environment and increase accessibility. However, despite the assistance provided by technology in daily activities, gaps still exist in the support needs of this population, suggesting the importance of future research and guidelines to make the digital world more inclusive.	It highlights the need to explore specific categories of AT for cognition such as alerts and biofeedback to meet the emotional and cognitive needs of this population. Barriers to technology adoption such as cost, clear instructions, and early benefits are also discussed, highlighting the importance of overcoming them to promote effective AT use by older adults with ASD.

Notes: Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Obsessive Compulsive Disorder (OCD), Intellectual Deficit Disorder (DID), Therapeutic Companion (AT), and Intelligence Quotient (QI).

Cognitive decline in adults with autism, along with possible accelerated neurophysiological aging, highlights the complexity of the interactions between aging and ASD.[51] Thus, the delicate balance between cognitive and social characteristics throughout the lives of adults with ASD reveals the need for a more in-depth and personalized understanding to effectively address the challenges associated with this disorder during aging.

Aspects related to suffering/mental illness

The relevance of psychiatric comorbidities in adults with ASD is an important element in adopting a functional approach, aiming to identify the underlying psychological suffering and adaptation strategies developed by these patients; furthermore, comorbidities seem to stand out for suffering in adulthood to the detriment of specific aspects of ASD.[32] Data were found on the prevalence of

mental health conditions, with anxiety and depression common in adults with autism regardless of age.[25] Furthermore, the connection between cognitive functioning and other aspects of daily life, such as psychological distress in autistic individuals, presents a complexity that must be considered when personalizing healthcare for each adult with ASD.[25]

Women with autism and people who live alone appear to be more susceptible to these conditions; therefore, adequate mental health resources essentially need to be available to this population.[22,38] Furthermore, the results also indicate that adults with autism are more likely to present with other psychiatric conditions such as depression and anxiety, although they are less likely to abuse alcohol and drugs.[49]

An alarming result was the high rate of suicidal ideation and suicide attempts among adults with autism.[34] The research highlights the concern about suicidal ideation and self-injury, which have a higher rate in the autistic population, placing it as a risk group when compared to the general population.[34] This highlights the importance of mental health care and providing appropriate support, particularly for those with bipolar and unipolar depression. Additionally, research has revealed that older adults with autism face difficulties coping with aging and often experience depression, anxiety, and sleep disturbances following the loss of loved ones.[23] This emphasizes the need for long-term care emphasizing safety, medical monitoring, and therapy to address emotional challenges.

Specifically, in women with autism, they present higher psychological and somatic complaints, especially related to autism. Quality of life was found to be lower in individuals with clinical cutoff points indicative of depression.[41]

The effect of comorbidities goes beyond psychological issues and influences communication and daily life skills. Constipation, epilepsy, and chronic kidney disease are the most frequent comorbidities associated with the severity of ASD.[42] The importance of a functional approach is reiterated, highlighting that, in adulthood, the emphasis is on associated disorders and psychiatric comorbidities, rather than on the fundamental characteristics for the diagnosis of ASD.[32]

Intervention strategies to improve quality of life

Several strategies have been used to improve the quality of life of adults with ASD. Among these strategies, implementation of an evidence-based program designed to improve specific social and interpersonal skills in adolescents and young adults with ASD is particularly notable. Thus, the aim is to provide practical tools and strategies that not only reduce symptoms of anxiety and depression but also promote significant improvements in social skills. This program actively involves caregivers as social coaches, contributing to a more effective and widespread development of interpersonal skills in adult life.[18] Furthermore, these interventions are essential and require personalized support, given that we understand the daily challenges faced by young people and adults with ASD; specifically for women with autism, this personalization is even more essential given their biological and social differences.[20,22]

Within the scope of strategies to promote autonomy, individualized assessment and reduce polypharmacy,[23] the need for specific approaches is highlighted. From this perspective, therapies focused on executive functions, physical activities, and specialized medical monitoring, for example, contributing to individual well-being, and understanding the variability of ASD throughout life favors the guidance of individualized approaches.[19,42] Adaptive strategies such as emotional support and interventions focused on feelings of control were relevant when applied to different subgroups,[39] and a mental health-centered approach and ongoing support are key to addressing the challenges associated with aging and autism.[46] Thus, integration of these strategies offers promising avenues for addressing the needs of adults with ASD.[43]

Adults with ASD demonstrate less vulnerability to cognitive decline when they are better educated, although they face elevated risks of memory decline, especially long-term.[61] Mindfulness-based educational and stress reduction interventions benefit mental health-related quality of life, especially in women with ASD.[27] Furthermore, professional activities, such as employment and higher education, are linked to positive outcomes and subjective well-being in adults with ASD. Career status at age 18 was identified as a solid indicator of professional outcomes in adult life, which emphasizes the importance of precocious interventions.[31]

The relationship between greater social support and quality of life is also evident,[30] highlighting the importance of solid support networks for adults with autism, especially as they age. The practice of mindfulness—techniques that direct full attention to present-moment experiences—can also help adults with autism learn to recognize and regulate their emotions, which can help alleviate the symptoms of psychiatric conditions comorbid with autism.[27]

Furthermore, it is essential to develop a model of psychosexual well-being to better understand sexuality in this specific group.[47] Adults with ASD reported lower levels of sexual desire and engagement in sexual behaviors. However, sexual satisfaction did not differ significantly compared to that in neurotypical people.[28] This data reinforces the need for sexual education adapted to the specificities of people with ASD and the understanding of their unique sexual experiences.

DISCUSSION

The growth/aging of people with ASD remains a little-explored topic in the literature, contrary to its description in children,[9] which contributes to the persistence of obstacles related to the social and health demands of this population. Effective strategies

to improve quality of life include early interventions focused on the integrity of brain areas related to restrictive behaviors,[35] functional approaches considering psychiatric comorbidities, personalized adaptations,[32] and interventions based on mindfulness for emotional regulation.[27] Social support and support networks play a fundamental role in improving quality of life, especially during aging.[30] These strategies have the potential to promote a better quality of life in adults with ASD.

In the mid-20th century, autism was included in the diagnosis of adult schizophrenia,[62] because they had not yet had the individualization of the characteristics of a separate disorder with its particularities and assistance needs. Only in 2013, with the fifth edition of the *Diagnostic Manual of Mental Disorders*,[1] the American Psychiatric Association recognized the unification of psychiatric conditions described in the literature as ASD. Thus, understanding how adolescents, adults, and elderly adults experience autism directly contributes to promoting quality of life for this population.

In 2019, the World Health Organization, in its eleventh edition of the *International Statistical Classification of Diseases and Related Health Problems*,[63] unified ASD based on disorders reported in previous versions and subdivided it according to the presence or absence of intellectual disability and functional language impairment. From this perspective, given that ASD has specificities for each group of individuals, understanding such singularities is essential for individualized and assertive treatment, which helps in functional development, cognition and sociability,[64] which are fundamental factors for maintaining the mental health of people with autism.

One clinical trial with young adults with ASD[18] was successful in developing social skills and reducing anxiety and depressive symptoms among the intervention group based on a treatment focused on training interpersonal behavioral skills, with a satisfaction rate of 76.57% among study participants, with an average age of 23.5 years. This demonstrates how improving sociability directly influences the lives of adults with ASD, since even with communicative difficulties, interpersonal relationships are a part of the lives of people with autism.[65]

Another study, covering this age group, found higher rates in variables related to happiness among a group of people aged 18–28 with ASD who had a job, possibly for the opportunity to contribute and establish social contact with individuals in their community.[31] In addition to quality of life, social reciprocity in people with autism potentially influences their mortality, given that it is directly related to adaptive behavior and self-sufficiency.[50] This point of social life must be introduced into the lives of people with autism to explore their cognitive potential, considering that aspects of verbal and visual memory of individuals with ASD may be similar to those of neurotypical people. However, it can manifest in different talents in each individual, with the potential for maturity through quality interpersonal relationships.[13] Therefore, despite the specificities of communication between adults with ASD, the establishment of affective/social bonds is important for the well-being of this population.

Associated with these strategies, the recognition of depressive symptoms in individuals with ASD and provision of adequate support constitute a fundamental strategy to optimize the health of this population, especially because of the greater risk of suicidal ideation and self-harm among people with ASD, which are fundamental factors for negative outcomes of the condition. suffering psychiatric.[34] In this sense, in addition to strengthening the family nucleus and support network of autistic adults, self-care practices, such as the implementation of leisure programs, physical activity, games and crafts, must be encouraged, in addition to practices that address spirituality and mindfulness.[66] This speaks directly to the need of adults and elderly adults with ASD for emotional and cognitive self-knowledge, considering that they represent a risk group for psychiatric disorders such as anxiety and depression, especially with age, which can increase the risk of suicide.[28]

In this sense, improved sleep quality is directly related to lower rates of suicidal ideation. Additionally, regular physical exercise is a protective factor against negative outcomes due to comorbidities. These practices have presented increasing benefits over the years, which can contribute to quality aging in people with ASD.[67] Furthermore, a sense of belonging, artistic expression, and spirituality are effective for mental health care.[10]

Art therapy, as a collective therapeutic strategy, contributes to the expression of feelings and thoughts, so that the inclusion of people with ASD in community-based services can contribute to the development of skills, social interaction, bonding, construction of perspectives of existence with and despite of the diagnosis(es).[68] Together, such aspects of daily life must be addressed in the therapeutic plan for this population, considering the benefits to their mental health and quality of life.

In line with the social deficit in autism, the perception of topics such as aging and death is also affected by this disorder. Specifically among elderly adults, the danger of rupture and abandonment, especially during periods of loss of family members, illness, and the advent of old age, represent important risk factors for depression, which is often confused with premature aging, added to possible dietary symptoms, with an impact on greater vulnerability of this population group.[32] However, daily difficulties can be managed with the use of currently available technologies that meet their needs, such as the use of the Global Positioning System (GPS), virtual reminders, messaging applications and headphones, capable of promoting the adaptation of elderly adults with ASD to daily life, providing autonomy by minimizing cognitive limitations that may impose themselves, such as the decline of visual memory and functionality.[57,60] This does not require interventions for the

prevention of emotional complexities that arise with the advent of aging, a phase in which family support and medical and psychological support are essential.

Questions about sex and sexuality were also addressed in some of the analyzed studies. Even though this field of research is small within ASD, people with autism clearly experience sexuality in a particular way, with unique experiences of the perception of sensuality, which is in dissonance with commonly guided sexual education, which is aimed at neurotypical individuals and rarely discusses self-perception.[47] In addition to self-recognition of sex and sexuality, elucidating issues related to sexual vulnerability and interpretation of one's own and other people's body signs becomes a fundamental tool for the social development of people with autism, avoiding the infantilization of this population, and encouraging their autonomy.[69]

Furthermore, addressing self-recognition of gender identity is also a benefit of sex education for individuals with ASD, considering that intimate issues can bring greater complexity to the social experience of these people, especially for transgender individuals, who often live with prejudice and the challenge of family acceptance, which can feed self-stigma.[70] This phenomenon further aggravates the weaknesses in the process of growth and well-being of people with autism, which demands special attention from the social nucleus and healthcare team.

Considering the diversity of issues that permeate the adult experience of ASD, discussing strategies appropriate to individual reality is essential for improving quality of life in the process of growth and aging.

As this study is a literature review, limitations of the included studies may have impacted their results. In this sense, there is a low sampling rate in a considerable number of articles, often associated with the heterogeneity or diagnostic simplification of the individuals analyzed, in addition to the absence of control groups, which makes it difficult to generalize the results to a portion of the research. Other highlights are the cross-sectional approach in the methodology of some studies, limited information on changes over time, and the lack of studies conducted in developing countries.

CONCLUSION

This integrative review reveals that adults with autism show strengths in verbal comprehension, perceptual reasoning, and theory of mind but face challenges such as reduced processing speed, sensory hypersensitivity, and difficulties in empathy and motor skills. They are more vulnerable to anxiety, depression, and suicidal ideation; however, they report similar sexual satisfaction as neurotypical individuals and lower substance abuse rates.

Effective strategies to enhance quality of life include evidence-based social skills programs, therapies for executive functions, physical activities, mindfulness interventions, and opportunities for education and employment. These approaches have contributed to the improvement of well-being and cognitive health over time.

This review emphasizes the importance of lifelong mental health support and tailored sex education for adults with autism. It also highlights the need for more research from developing countries on adult sexuality in autism to guide clinical practice and ensure comprehensive context-specific care throughout life.

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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.

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