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Perspectives and relevance of evidence-based medicine in Brazil*

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Scarcity of resources and their inefficient use form the basis of the difficulties of the Brazilian healthcare system. Practical application of evidence-based medicine (EBM) is grounded in identifying the best scientific evidence regarding the efficacy, effectiveness, efficiency and safety of every intervention, whether it is of diagnostic, therapeutic or preventive nature. Efficiency refers to doing more technically with fewer resources; efficacy refers to doing this under ideal conditions; and effectiveness refers to doing this in contexts that take into account patients' real conditions and their circumstances. In turn, safety requires proper proof and assurance that every decision will bring more benefit than harm to individuals and to society.

There is absolutely no doubt that the impact of EBM has improved efficiency within the field of healthcare worldwide. In Brazil too, adoption of the concepts of EBM by the Ministry of Health has been shown to avoid waste, of the order of tens of billions of reais, and has brought major benefits for the population.[1,2] Moreover, this movement has contributed greatly towards the development of basic research and research applied to clinical medicine. This has been translated into better results from finite investments in scientific investigations in the field of healthcare. This must not remain unnoticed within Brazilian research funding agencies.

It is therefore of paramount importance to stimulate teaching of EBM within undergraduate courses within the field of healthcare. In Brazil, fewer than 20% of medical schools include EBM among the concepts forming part of the curriculum![3] It is rare for medical schools to have a sector for EBM, yet this is fundamental for its propagation and implementation. EBM has immense value for constructing critical awareness regarding healthcare interventions in the initial phases of the course, such that students will gain the ability to better analyze scientific communications, whether these are in published data or at congresses in which they participate. From the time when students start to do research, they will incorporate the fundamentals of EBM into a wide variety of fields of healthcare and will translate their knowledge into technical production.

Furthermore, over the last few years, hundreds of postgraduate students of EBM have earned their degrees in Brazil. These professionals comprise not only doctors but also psychologists, nurses, dentists, physiotherapists, librarians, journalists, lawyers, prosecutors, biologists, pharmacists, speech therapists and many others. In our setting, we now have a critical mass with the capacity to start to disseminate this culture and equip our teaching institutions. We need to move forward in this regard, given the potential benefits of EBM for improving our social structure.

Technology and innovation are the buzzwords today. However, there is a need for careful analysis on the proof (or evidence), to demonstrate that incorporation of these technologies and innovations is efficient and safe. Rationality in acquiring new technologies is a fundamental premise, particularly when application of public resources is involved.

For more than two decades, the São Paulo Medical Association (Associação Paulista de Medicina) has focused its attention on EBM. It has striven towards consolidating the culture that this movement represents, and has done so not only for the benefit of Brazilian medicine but also, above all, to ensure full rights to quality healthcare for our population, in other words, evidence-based healthcare rights and implementation.

REFERENCES

1. Andriolo RB, Puga ME, Belfort R Jr, Atallah AN. Bevacizumab for ocular neovascular diseases: a systematic review. Sao Paulo Med J. 2009;127(2):84-91. PMID: 19597683; doi: 10.1590/S1516-31802009000200006.
2. Elias FT, Silva EN, Belfort R Jr, Silva MT, Atallah ÁN. Treatment Options for Age-Related Macular Degeneration: A Budget Impact Analysis from the Perspective of the Brazilian Public Health System. PLoS One. 2015;10(10):e0139556. PMID: 26457416; doi: 10.1371/journal.pone.0139556.
3. Puga ME. Mapeamento do ensino de Medicina baseada em evidências nos currículos das escolas médicas do Brasil [thesis]. São Paulo: Universidade Federal de São Paulo (UNIFESP); 2007. Available from: http://bdtd.ibict.br/vufind/Record/UFSP_fbdce57aae649f899e610d3350e18d1f. Accessed in 2018 (Oct 11).

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Characteristics of total laparoscopic hysterectomy among women with or without previous cesarean section: retrospective analysis

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ABSTRACT

BACKGROUND: The number of hysterectomized patients with previous cesarean sections (CSs) has increased due to increasing CS rates. A previous history of CS has been demonstrated to be an important risk factor for major complications in total laparoscopic hysterectomy. The aim here was to evaluate the major complications and safety of TLH in patients with previous CS.

DESIGN AND SETTING: Retrospective analysis in a tertiary-level center.

METHODS: The medical records of 504 total laparoscopic hysterectomy patients operated between May 2013 and May 2017 were reviewed retrospectively. Data on age, parity, surgical indications, duration of operation, length of hospital stay, histopathological diagnosis and major intra and postoperative complications were gathered. The patients were categorized into two groups according to their CS history, namely those with and those without previous CS. Major complications were defined as the presence of lower urinary tract injury (bladder or ureter injury), enterotomy/colostomy, bowel serosal injury or vascular injury.

RESULTS: There was no difference between the groups in terms of parity, duration of operation, hospital stay or pre and postoperative hemoglobin levels. The conversion rates to laparotomy in the previous CS and no CS groups were 2% and 1.7%, respectively. The rates of major complications in the previous CS and no CS groups were 5% and 1.3%, respectively, and these results did not differ significantly ($P > 0.05$).

CONCLUSION: TLH could be performed safely in the previous CS group, since the complication rate was not different from that of the patients without previous CS.

INTRODUCTION

Hysterectomy is one of the most commonly performed gynecological operations. It is carried out because of a variety of indications, such as presence of dysfunctional uterine bleeding, myoma uteri, adenomyosis and adnexal mass. Hysterectomy can be performed using abdominal, vaginal, laparoscopic or robotic methods. According to the results from a study performed in the United States, the incidence rates for hysterectomies using abdominal, vaginal and laparoscopic methods are 66%, 22% and 12%, respectively.[1]

There is still no consensus on which of these approaches is the optimum surgical method for hysterectomy. Abdominal hysterectomy is the most frequently performed approach, but current clinical practice mandates that, when appropriate, the surgical method should be vaginal rather than abdominal, since the former is associated with better outcomes and lower complication rates. Moreover, when vaginal hysterectomy is not feasible or not indicated, the surgical method should be laparoscopic, because total laparoscopic hysterectomy (TLH) provides a faster return to normal activity, shorter hospital stays, lower intraoperative bleeding and fewer wound infections, compared with abdominal hysterectomy. However, longer operating times and higher incidence of urinary system damage are seen in laparoscopic hysterectomies.[2]

Because of the gradually increasing rates of cesarean sections (CSs) over the last two decades, the number of hysterectomized patients with previous CS has increased. In a recent review article, previously performed CSs were demonstrated to be an important risk factor for lower urinary tract injuries, and the recommendation that abdominal hysterectomy might be preferable for these patients was emphasized.[3] TLH may be technically difficult in patients with previous CSs, due to surgical adhesions, and is associated with a higher risk of perioperative complications.[4]

OBJECTIVES

To identify the characteristics of women undergoing total laparoscopic hysterectomy, and the frequency of peri and postoperative complications, comparing those with or without previous cesarean section.

METHODS

Study design, setting and participants

This was a retrospective analysis that included all patients who had undergone TLH in our hospital between May 2013 and May 2017. The medical records of 695 patients who underwent TLH were reviewed. Among these patients, 150 were excluded because of occurrences of tubo-ovarian abscess, endometriosis, pelvic tuberculosis, pelvic organ prolapses, history of previous abdominal surgeries or gynecological malignancies. Another 40 cases were excluded because of insufficient data in the medical records. The study was approved by the local ethics committee (date: July 31, 2017; approval number: 2017-08-26).

The patients were classified into two groups according to whether or not they had previously undergone CS. Based on their history of CSs, the patients' medical records were compared with regard to age, parity, body mass index, surgical indications, duration of operation, length of hospital stay and major intra and postoperative complications. Major complications were defined as the presence of lower urinary tract injury (bladder or ureter injury), enterotomy/colostomy, bowel serosal injury or vascular injury.

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences, version 20 (SPSS Inc.). The chi-square and Student's t tests were used for statistical comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

This study was completed with 505 patients. Using Yada-Hashimato's study as a guide, a power analysis was performed and a total sample size of 500 was estimated as required to obtain a power of 80% for difference between two independent groups (0.4 effect size and 0.05 α error).

All the patients were hospitalized one day before the operation and underwent bowel preparation with liquid enema, overnight before the surgery. Fluid intake was withheld for at least eight hours before the surgery. All the patients were catheterized through the urethral route before the surgery was undertaken, and the catheters were removed on the first postoperative day. The duration of the operation was defined as the time that elapsed from the induction of anesthesia to its termination.

In all cases that underwent TLH, the standard surgical technique was used. In most of the patients, a primary trocar with a caliber of 10 mm was directly inserted through the umbilicus or supraumbilical region, according to the size of the uterus. In situations of failure of access with the primary trocar, an open technique was used. In addition, a total of three accessory trocars with a caliber of 5 mm were inserted suprapubically through the midline and at points on the left and right sides of the midline.

The round ligaments were cauterized and cut bilaterally. The infundibulopelvic ligament was cauterized, and it was then cut in cases requiring oophorectomy. In contrast, in patients whose ovaries would be spared, the utero-ovarian ligaments were cauterized and cut. Bilateral salpingectomy was performed. The anterior and posterior peritoneum was opened. The bladder was dissected, beginning from the left lateral aspect, and was pushed downward.

After these steps, the uterine arteries were skeletonized and cauterized bilaterally. The vaginal manipulator was retracted to identify the cervicovaginal junction. Colpotomy was performed on the rim of the Clermont-Ferrand uterine manipulator, using a monopolar cautery, and the specimen was removed by means of the vaginal route. Finally, the vaginal vault was closed laparoscopically using a barbed no. 2 suture in all cases.

The TLH procedure was performed by eight surgeons who had laparoscopic training certificates or who had performed an average of 30 cases with an experienced surgeon.

It was found that the cases with a history of CS were significantly younger than the cases without previous CS ($P = 0.01$). Apart from the patients' ages, the clinical characteristics of the groups were comparable (**Table 1**). Body mass index, parity, surgical indications, duration of operation and duration of hospitalization were similar between the groups. 67% of the patients with previous CS had undergone one CS, 25% had undergone two CSs and 8% had undergone three CSs. Uterine myoma was the most frequent indication for surgery in both groups; other indications and their frequencies are shown in **Table 2**. No difference between the two

Table 1. Clinical characteristics of patients with no cesarean section (CS) and previous CS

	No CS (n = 446)	Previous CS (n = 59)	P-value
Age (years)	49 ± 6.3	46.8 ± 5.5	0.015
Gravida (n)	4.3 ± 2.5	4.2 ± 2.6	0.753
Parity (n)	3.5 ± 2.1	3.4 ± 2.2	0.825
Body mass index (kg/m^2)	31.7 ± 5.2	32.7 ± 5.7	0.220
Preoperative hemoglobin (g/dl)	11.5 ± 1.6	11.7 ± 1.5	0.331
Postoperative hemoglobin (g/dl)	10.5 ± 1.5	9.9 ± 1.2	0.785

Data are expressed as mean (± standard deviation).

groups was detected in terms of major complications (**Table 2**). In the multivariate logistic regression analysis, the effect of age on complications was not statistically significant (P = 0.36; RR: 1.03; 95% CI 0.96-1.11).

During TLH, the conversion rates to laparotomy in the previous CS and no CS groups were 2% and 1.7%, respectively. The rates of major complications in the previous CS and no CS groups were 0.16% (n = 6) and 1.21% (n = 3), respectively, and these rates did not differ significantly between the groups (P > 0.05).

In the no CS group, one case of bladder injury, three of bowel injury and two of major vessel injury occurred. In two patients, small retroperitoneal hematomas were observed. Since these were of limited extent, expectant management was implemented. A 3-cm bladder injury defect was repaired laparoscopically. One case of ileum injury, probably due to direct trocar insertion, was detected on the third postoperative day and was treated by means of ileostomy. One case of bowel injury in the rectosigmoid area was detected on the third postoperative day and primary repair was performed. One case of bowel injury in the serosa of the rectosigmoid area was detected intraoperatively and was sutured. In the previous CS group, one case of bladder injury, one of ureter injury and one of bowel injury occurred. One case of bowel injury on the serosal surface of the rectosigmoid colon that was detected intraoperatively was repaired by means of laparoscopic suturing. In addition, a 2-cm bladder injury defect was sutured laparoscopically. One case of ureteral injury was treated by means of double J stent insertion. No vaginal cuff dehiscence occurred in either group.

Table 2. Surgical outcomes relating to TLH among patients with no cesarean section (CS) and previous CS

	No CS (n = 446)	Previous CS (n = 59)	P-value
Type of surgery (n, %)			
TLH	225 (50.4)	33 (55.9)	0.428
TLH + BSO	221 (49.6)	26 (44.1)	
Indications (n, %)			0.662
Myoma uteri	270 (60.5)	34 (57.6)	0.668
Abnormal bleeding	84 (18.8)	14 (23.7)	0.372
Endometrial hyperplasia	52 (11.7)	8 (13.6)	0.672
Others	40 (9)	3 (5.1)	0.375
Duration of operation (min)	184.8 ± 52.9	183.7 ± 59.7	0.880
Hospital stay (day)	2.7 ± 1.9	2.7 ± 1.2	0.969
Major complications (n, %)	6 (1.3)	3 (5.0)	0.218
Bladder injury	1 (0.2)	1 (1.7)	0.220
Ureter injury	0	1 (1.7)	0.117
Bowel injury	3 (0.6)	1 (1.7)	0.393
Vessel injury	2 (0.5)	0	0.606
Conversion to laparotomy	9 (2.0)	1 (1.7)	0.669

Data are expressed as mean (± standard deviation) or proportions; TLH = total laparoscopic hysterectomy; BSO = bilateral salpingo-oophorectomy.

DISCUSSION

Many surgeons consider that previous experience of CS increases the incidence of complications relating to hysterectomy. Since TLH allows improved exploration and an opportunity for more delicate dissection, we evaluated the reliability and safety of TLH in patients who had previously undergone CSs. We did not find any significant difference in terms of major complications between the CS and no CS groups. The results from this study demonstrated that TLH is not a risk factor regarding major complications or lower urinary system injuries in cases with a history of CS. In cases with a history of CS, TLH may be performed safely and the complications that may occur, especially those relating to lower urinary system injuries that are managed intraoperatively, are not associated with long-term morbidities.

Moreover, patients in the previous CS group were significantly younger than the cases without CS. This finding is consistent with the results from previous studies.[5,6] However, this age difference did not have any impact on complication rates, after adjustment for age in the statistical analysis.

According to the results from an analysis on surgical data conducted in the United States in 2010, the incidence rates for abdominal, laparoscopic and robot-assisted hysterectomy were reported as 65%, 16% and 17%, respectively.[7] In suitable cases, the minimally invasive vaginal or laparoscopic approach should be preferred, considering the advantages of these approaches over abdominal hysterectomy.[8] The choice of the route for hysterectomy is affected by many conditions, such as the size and configuration of the uterus and vagina, ease of accessibility (e.g. in situations of descensus or pelvic adhesions), presence of an extrauterine disease, need for additional surgery, surgeon's experience and clinic's technical facilities.[9,10]

No difference between the two groups in this study was observed in terms of major complications (CS group, 5.1%; no CS group, 1.3%). The prevalence rates for bowel injury were 0.6% and 1.7% of the cases with and without previous CS, respectively. In two cases, an intraoperatively detected serosal defect was treated by means of primary suturing, via the laparoscopic approach. In one case, a serosal defect was closed as a primary procedure on postoperative day 3. One case of an ileal defect that was thought to be related to the direct trocar access was detected on postoperative day 3 and repaired with ileostomy.

Most of the major vessel and bowel injuries occurred during intra-abdominal access using a Veress needle or primary trocars.[6,7] Although the risk of bowel injury is less than 0.5%, it needs to be borne in mind that if the small bowel is damaged and this is not observed early enough, this condition can increase mortality rates.[9] The conversion rates to laparotomy in the previous CS and no CS groups were 2% and 1.7%, respectively. The factors that affected conversion to laparotomy included a large uterus that hindered

direct vision, laterally located myomas complicating the access to the uterine vessels and previous abdominopelvic surgery.[11]

It is known that previous pelvic surgery may impair the normal anatomy through effacement of the surgical planes. In CSs, adhesions that form between the bladder and uterus complicate dissection during mobilization of the bladder away from the uterus. In cases with previous CS, surgeons often refrain from performing vaginal and laparoscopic hysterectomies for fear of increasing the complication rates.[12,13] In a recent cohort study, it was revealed that patients with a history of CS carried a greater risk of hysterectomies over the long term. Moreover, compared with patients who have given birth via vaginal delivery, those with a history of CS more frequently require reoperation after hysterectomy, since they have higher rates of peri and postoperative complications.[14]

A history of CS is the most frequently encountered risk factor for bladder injuries.[15] The prevalence of bladder injuries has been reported to range between 0.7% and 1.5% among patients who have undergone TLH.[6,16] In our study, bladder injury was only seen in one patient (1.7%), who had a previous history of CS, and no statistically significant difference was detected in comparison with those without previous CS. This case of bladder injury was detected intraoperatively and repaired laparoscopically. In cases with TLH, the prevalence of ureteral injuries ranges between 0.04% and 0.70%, representing one-third of the prevalence rate of bladder injuries.[17,18]

Ureteral injuries may be related to the use of electrosurgery for tissue dissection and hemostasis during laparoscopic interventions.[14] In our study, ureteral injury was detected in one patient in the CS group, while it was not observed in the no CS group. In this case of ureteral injury, ureteral stricture developed secondarily to thermal injury, which was treated through implantation of a double J stent that was left in situ for three months, and no additional surgery was required.

This study had some important limitations. These included its retrospective design and inadequate number of cases in the CS group for evaluation of the rarely seen complications. Since TLHs were performed by more than one surgeon, surgical performance bias might be another limitation of the study. A further limitation was that we did not analyze intraoperative complications according to the level of surgeon training or the surgical case volume performed by the surgeons. In addition, yet another limitation was that we did not evaluate the effect of the number of CSs on the complication rates.

CONCLUSION

TLH can be performed safely in cases with a history of CSs, since major complication rates were not different from that of the patients without previous CS. Moreover, major complication rates, duration of operation, blood loss, postoperative hospital stays and conversion rate to laparotomy did not differ significantly between patients with and without CS.

REFERENCES

1. Wu JM, Wechter ME, Geller EJ, Nguyen TV, Visco AG. Hysterectomy rates in the United States, 2003. Obstet Gynecol. 2007;110(5):1091-5. PMID: 17978124; doi:10.1097/01.AOG.0000285997.38553.4b.
2. Nieboer TE, Johnson N, Lethaby A, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev. 2009(3):CD003677. PMID: 19588344; doi:10.1002/14651858.CD003677.pub4.
3. Rooney CM, Crawford AT, Vassallo BJ, Kleeman SD, Karram MM. Is previous cesarean section a risk for incidental cystotomy at the time of hysterectomy? A case-controlled study. Am J Obstet Gynecol. 2005;193(6):2041-4. PMID: 16325612; doi:10.1016/j.ajog.2005.07.090.
4. Wright JD, Herzog TJ, Tsui J, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol. 2013;122(2 Pt 1):233-41. PMID: 23969789; doi:10.1097/AOG.0b013e318299a6cf.
5. Committee on Gynecologic Practice Committee Opinion No 701: Choosing the Route of Hysterectomy for Benign Disease. Obstet Gynecol. 2017;129(6):e155-e159. PMID: 28538495; doi:10.1097/aog.0000000000002112.
6. Llarena NC, Shah AB, Milad MP. Bowel injury in gynecologic laparoscopy: a systematic review. Obstet Gynecol. 2015;125(6):1407-17. PMID: 26000512; doi:10.1097/aog.0000000000000855.
7. Sandadi S, Johannigman JA, Wong VL, et al. Recognition and management of major vessel injury during laparoscopy. J Minim Invasive Gynecol. 2010;17(6):692-702. PMID: 20656569; doi:10.1016/j.jmig.2010.06.005.
8. Leonard F, Chopin N, Borghese B, et al. Total laparoscopic hysterectomy: preoperative risk factors for conversion to laparotomy. J Minim Invasive Gynecol. 2005;12(4):312-7. PMID: 16036189; doi:10.1016/j.jmig.2005.05.015.
9. Munro MG, Parker WH. A classification system for laparoscopic hysterectomy. Obstet Gynecol. 1993;82(4 Pt 1):624-9. PMID: 8377992.
10. Poindexter YM, Sangi-Haghpeykar H, Poindexter AN, 3rd, et al. Previous cesarean section. A contraindication to vaginal hysterectomy? J Reprod Med. 2001;46(9):840-4. PMID: 11584488.
11. Lindquist SAI, Shah N, Overgaard C, et al. Association of Previous Cesarean Delivery with Surgical Complications after a Hysterectomy later in Life. JAMA Surg. 2017;152(12):1148-55. PMID: 28793157; doi:10.1001/jamasurg.2017.2825.
12. Soong YK, Yu HT, Wang CJ, Lee CL, Huang HY. Urinary tract injury in laparoscopic-assisted vaginal hysterectomy. J Minim Invasive Gynecol. 2007;14(5):600-5. PMID: 17848321; doi:10.1016/j.jmig.2007.05.004.
13. Lim S, Lee S, Choi J, et al. Safety of total laparoscopic hysterectomy in patients with prior cesarean section. J Obstet Gynaecol Res. 2017;43(1):196-201. PMID: 27928849; doi: 10.1111/jog.13191.
14. Sinha R, Sundaram M, Lakhotia S, Hedge A, Kadam P. Total laparoscopic hysterectomy in women with previous cesarean sections. J Minim Invasive Gynecol. 2010;17(4):513-7. PMID: 20621012; doi: 10.1016/j.jmig.2010.03.018.

15. Wong JMK, Bortoletto P, Tolentino J, Jung MJ, Milad MP. Urinary Tract Injury in Gynecologic Laparoscopy for Benign Indication: A Systematic Review. Obstet Gynecol. 2018;131(1):100-8. PMID: 29215524; doi: 10.1097/aog.0000000000002414.
16. Adelman MR, Bardsley TR, Sharp HT. Urinary tract injuries in laparoscopic hysterectomy: a systematic review. J Minim Invasive Gynecol. 2014;21(4):558-66. PMID: 24462595; doi: 10.1016/j.jmig.2014.01.006.

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Accuracy of praxis test from Cambridge Cognitive Examination (CAMCOG) for Alzheimer's disease: a cross-sectional study

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ABSTRACT

BACKGROUND: Praxis impairment may be one of the first symptoms manifested in dementia, primarily in cortical dementia. The Cambridge Cognitive Examination (CAMCOG) evaluates praxis, but little is known about the accuracy of CAMCOG for diagnosing dementia. The aims here were to investigate the accuracy of praxis and its subitems in CAMCOG (constructive, ideomotor and ideational subitems) for diagnosing Alzheimer's disease (AD) among elderly patients.

DESIGN AND SETTING: Cross-sectional study on community-dwelling elderly people.

METHODS: 158 elderly patients were evaluated. CAMCOG, Mini-Mental State Examination and Pfeffer Functional Activities Questionnaire were used. ROC curve analysis was used to establish cutoff points.

RESULTS: The total scores for praxis and the constructive subitem presented significant differences ($P < 0.0001$) between healthy elderly people and AD patients. Stage of dementia (clinical dementia rating, CDR = 0, 1 and 2) showed that total and constructive praxis can be used to classify the stages of dementia (mild and moderate cases), i.e. constructive praxis classified 88% of the patients with mild dementia ($P < 0.0001$) while total praxis classified 56% with moderate dementia. Comparison of normal controls (NC) and mild dementia cases showed specificity of 71% and sensitivity of 88% (AUC = 0.88; $P < 0.0001$).

CONCLUSION: Some praxis subtests can have higher predictive diagnostic value for detecting Alzheimer's disease in mild stages (total praxis AUC = 0.858; $P < 0.0001$; constructive AUC = 0.972; $P < 0.0001$). Constructive praxis as measured using CAMCOG may contribute towards diagnosing dementia, because occurrence of impairment of praxis may help in recognizing an evolving dementia syndrome.

INTRODUCTION

The structured interview of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[1] is widely used by Brazilian professionals and has been validated by Bottino et al. for the Portuguese language.[2] Its cognitive tasks are called the Cambridge Cognitive Examination (CAMCOG) and evaluate several functions, such as memory, praxis, attention, orientation, perception, language and others.[1] Aprahamian et al.[3] and Nunes et al.[4] (2008) found similar data regarding the accuracy of diagnostic investigation of dementia using CAMCOG. Sensitivity and specificity, respectively, were 100% and 95%. Even the reduced version of the cognitive battery, with only half of the items (CAMCOG-R), showed 98% sensitivity and 100% specificity for diagnosing Alzheimer's disease (AD). In addition to use of CAMCOG for investigation of clinical conditions, Paradela et al.[5] described its applicability in the context of epidemiological investigation. These authors pointed out the reliability of the total CAMCOG score: the patients were reassessed over a period of time and, even at different stages of dementia, the reliability of this score was maintained after analysis on internal consistency.

The relevance of praxis tasks as a form of reliable screening in relation to subcortical dementia such as major vascular neurocognitive disorder has been well documented in the literature.[6-9] Evaluation of praxis in cases of subcortical dementia is important because this may demonstrate impairment in relation to execution of the tests; for example, through drawings (constructive task), gestures (ideational task) or a sequence of tasks (ideomotor task). This impairment is often inversely proportional to subcortical cerebral injury, thus allowing clinicians to provide a more accurate prognosis for cognitive decline and functional impairment.[8-12]

In 1920, Lipeman studied 84 patients who suffered strokes and discovered that, in addition to aphasia, the patients also had impairments of motor skills such as debilitated copying and imitative gestures.[13] Moreover, regarding more precise aspects of the diagnosis, CAMCOG has contributed towards evaluation of total praxis and its subitems through showing the relevance of some studies that have indicated that impairment of praxis abilities confirms that there is a risk of rapid evolution to severe cases of dementia.[10,14]

OBJECTIVE

The objective of the present study was to investigate the accuracy of the praxis test of CAMCOG for diagnosing Alzheimer's disease among elderly people.

METHODS

Study design

This cross-sectional study was conducted in the city of Jundiaí, state of São Paulo. It was previously approved by the local institutional ethics committee (CEP number 853.742 and CAAEE number 34669514.0.000.5435) on January 1, 2015. All procedures were implemented in accordance with the Helsinki Declaration.

Participants

The size of a representative sample was calculated as at least 101 participants (more details can be obtained in Fiel).[15] Patients of both sexes, over 60 years of age, were evaluated. The initial sample comprised 237 elderly people, i.e. all the consecutive patients admitted between 2015 and 2017), who underwent anamnesis and neuropsychological evaluation. After the exclusion criteria had been applied, the study population comprised 158 participants. The following inclusion criteria were used: the participants needed to be men and women over 60 years of age, with one year of schooling or more; needed to have given their consent to voluntarily participate in the study; and needed to have signed the informed consent form.

In previous studies, the following exclusion criteria were adopted: presence of severe dementia (clinical dementia rating ≥ 3); history of stroke (according to magnetic resonance imaging examination); paralysis in both hands; depressive symptoms (scores ≥ 5 points on the Geriatric Depression Scale);[16] walking using short steps; tremors and muscle rigidity that might suggest Parkinsonism; major tremors; visual and auditory difficulties; and neuropsychological reports of not being able to read and write (illiteracy).

AD participants were diagnosed with major neurocognitive disorder due to Alzheimer's disease in accordance with DSM-5[17] and NIA-AAW.[18]

Praxis evaluation from CAMCOG

The CAMCOG cognitive battery was inserted as part of the CAMDEX investigation of mental disorders.[2] CAMCOG has 67 cognitive items divided into subitems of memory, language, praxis, abstract thinking, calculus, attention, orientation, perception and gnosis.[1,2] Application of the CAMCOG battery includes the Mini-Mental State Examination screening test.

CAMCOG evaluates three forms of praxis: constructive, ideational and ideomotor. In the constructive form of praxis, copies of figures such as a house in 3D and a pentagon are evaluated. In the ideomotor form of praxis, patients need to be able to perform learned tasks when receiving certain objects, for example, picking up a piece of paper and putting it inside an envelope. In the ideational form of praxis, patients need to be able to perform tasks in the correct order, such as making a "good-bye" movement with one hand or tying shoelaces.[19,20]

In this study, we used the CAMDEX structured interview subitems of the CAMCOG cognitive sections. These evaluate praxis by comparing the performance of elderly people with a diagnosis of AD with that of healthy elderly people (CG). The CAMCOG subitems for evaluating praxis were analyzed separately. These subitems were the following:

- **Constructive praxis**, in which the patient is asked to copy figures depicting a pentagon (1 point), a spiral (1 point), a house in 3D (1 point) and a clock (3 points). The total score for this subitem is 6 points;
- **Ideational praxis**, in which the patient is asked to place a paper inside an envelope (1 point);
- **Ideomotor praxis**, in which the patient is asked to follow the examiner's commands. Three gestures are requested through these verbal commands, and the patient needs to be able to make the correct movements for them: a "goodbye" gesture; a movement of the fingers to indicate the action of cutting with a pair of scissors; and a gesture to show brushing the teeth (total score 5 points).

The total score possible for the praxis items was 12 points and a low score indicated impairment (apraxia).

Data collection

All the cognitive tests were performed in a single session, lasting around 110 minutes. The diagnosis was determined after clinical, laboratory, neuroimaging and neuropsychological analyses. The patients underwent the Cambridge Cognitive Examination (CAMCOG),[1,2] Mental State Mini-Examination (MMSE)[21] (which is included in the CAMCOG battery), Geriatric Depression Scale questionnaire with 15 items[16] and Pfeffer Functional Activities Questionnaire (PFAQ).[22] It should be noted that the Geriatric Depression Scale was only applied as

an exclusion criterion (depressive symptoms). The CAMCOG cognitive battery and the MMSE screening test were the instruments used to evaluate cognitive functions. The PFAQ was applied to obtain information about the patients' performance in activities of daily life.

Statistical methods

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 15.0). Normality tests were performed, and occurrences of nonparametric distribution were indicated. Schooling, age and gender were analyzed in terms of percentages, means and standard deviations. To evaluate the effects of age, schooling and sex, correlations were made by controlling for these variables through Spearman analysis. Student's test was performed for age and the chi-square test (χ^2) was used between schooling and sex. For all analyses, the significance level was established as 5%.

Associative statistics between praxis and the memory subitems from CAMCOG were assessed. Correlations were made between praxis and diagnostic groups (CG and AD), separated according to schooling and age. As in Alzheimer's disease, one of the earliest functions to be impaired is memory,[17] and we chose to correlate this function from CAMCOG with praxis and its subitems. For this, we used the sum of the memory subitems from CAMCOG, i.e. the sum of the remote, recall, recent and recognition memories. A total memory score was generated, and it was this total score that was used for the correlation analysis.

Accuracy analyses were used to investigate the CAMCOG praxis at each of the three levels of states of dementia: no dementia, mild dementia and moderate dementia. These were measured using the Clinical Dementia Rating (CDR) scale.

Analyses between the diagnostic groups (AD and CG) in relation to the cognitive tests were made using the Mann-Whitney test. Finally, the sensitivity and specificity of the cognitive instruments (MMSE and CAMCOG) and praxis (total, constructive and ideomotor praxis) were analyzed by means of the receiver operating characteristic (ROC curve) and, for this analysis, the MedCalc software, version 15.8, was used.

RESULTS

The 158 elderly subjects included in this study had a mean age of 78.62 years (minimum = 60, maximum = 97, standard deviation = 8.07) and 68.4% (n = 108) were female. Regarding schooling, 72.2% (n = 114) had had between 1 and 4 years, 12% (n = 19) between 5 and 8 years and 15% (n = 25) ≥ 9 years. 46.8% (n = 74) were diagnosed with Alzheimer's disease (AD) and 53.2% (n = 84) formed the CG. **Table 1** compares mean age, sex and schooling between the two groups. The sample was homogenous between the diagnostic groups (AD and CG) regarding the categorical variables (sex and education) and continuous variable (age).

We investigated the sensitivity and specificity data relating to the CAMCOG praxis item and its sub-items, from both diagnostic groups: CG and AD. **Table 1** describes the comparison between the two diagnostic groups in relation to the cognitive tests (MMSE, CAMCOG and praxis) and the subitems (constructive, ideational and ideomotor). There were lower means in the AD group in all cognitive tests except for the ideational and ideomotor subitems. It can be inferred that the MMSE ($P < 0.0001$), CAMCOG ($P < 0.0001$), total praxis ($P < 0.0001$) and constructive praxis ($P < 0.0001$) tests were able to statistically differentiate between the two diagnostic groups. Lower mean scores were observed in the group with the diagnosis of AD. It is important to note that the group with AD scored below the cutoff point for CAMCOG, which would be above 80 points. CAMCOG is considered to be the diagnostic tool for mental disorder among elderly people.[1,2] The statistical differences that were found between MMSE and CAMCOG were concordant with data in studies in the literature,[3,4,23] which emphasizes the high sensitivity and specificity of these instruments (MMSE and CAMCOG) for diagnostic investigation of AD.

The ideational ($P = 0.854$) and ideomotor ($P = 0.114$) subitems were not able to differentiate between the two groups. It can be inferred that both of these subitems have a ceiling effect, i.e.

Table 1. Characteristics among diagnostic groups in relation to age, sex and schooling. Descriptive data from MMSE, CAMCOG, praxis (total score and sub-items) and PFAQ on 74 patients diagnosed with Alzheimer's disease (AD) and 84 healthy elderly people (control group, CG)

	CG	AD	P
Age (years)	77.73 (60-96) (± 8.66)	79.64 (60-97) (± 7.28)	*0.139
Sex			
Female	66.7%	70.3%	**0.628
Male	33.3%	29.7%	
Schooling			
1 to 4 years	71.4%	73%	
5 to 8 years	10.7%	13.5%	**0.730
> 9 years	17.9%	13.5%	
	Mean ± SD	**Mean ± SD**	
MMSE	27.45 ± 2.43	17.05 ± 4.25	**0.0001**
CAMCOG	89.9 ± 9.39	56.35 ± 13.84	**0.0001**
PFAQ	0.77 ± 1.97	19 ± 9.10	**0.0001**
Praxis (total)	10.82 ± 1.32	8.30 ± 1.86	**0.0001**
Constructive	5.63 ± 0.70	3.36 ± 1.54	**0.0001**
Ideational	0.95 ± 0.21	0.95 ± 0.22	0.854
Ideomotor	4.21 ± 0.89	3.99 ± 0.97	0.114

MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Cognitive Examination; PFAQ = Pfeffer Functional Activities Questionnaire; SD = standard deviation.
*P from Student t test; **P from chi-square test.

they provide satisfactory scores in both the healthy elderly group and the group with neurocognitive disorder (**Table 1**). Although Nagahamaet et al.[8] and Trojano et al.[9] showed statistically significant differences regarding the ideational and ideomotor subitems for identifying subcortical impairment, our findings indicate that in cases of predominantly cortical dementia, these subitems are preserved even in cases of evident disorder.

The ideational subitem consists of only one score (1 point for a correct result and 0 point for an erroneous result). On the other hand, the ideomotor subitem presents a maximum score of 5 points, but this task can be satisfactorily performed by patients with mild and moderate dementia because of the automation of the act (i.e. it can be done even with a lack of comprehension).[24,25] However, there were statistically significant differences in relation to the items of total praxis ($P < 0.0001$) and constructive praxis ($P < 0.0001$).

There was no correlation between the variables and the subitems of praxis. Only constructive praxis presented a tendency to be associated with the educational variable ($r = 0.23$; $P = 0.052$). As in Alzheimer's disease, one of the earliest functions to be impaired is memory, and we chose to correlate this function from CAMCOG with praxis and its subitems. Robust positive correlation coefficients between memory and total praxis ($r = 0.72$; $P < 0.0001$) and between memory and constructive praxis ($r = 0.71$; $P < 0.0001$) could be seen. A weak positive correlation between memory and ideomotor praxis ($r = 0.34$; $P < 0.0001$) was found. There was no correlation between memory and ideational praxis ($r = 0.17$; $P = 0.077$).

Table 2 shows that ideomotor praxis cannot differentiate between mild and moderate dementia. Moreover, it can be seen that total and constructive praxis can be used to classify the stages of dementia (mild and moderate cases), i.e. constructive praxis classified 88% of the patients with mild dementia while total praxis classified 56% with moderate dementia ($P < 0.0001$). Comparing the control group (NC) and moderate dementia group (CDR = 2), it can be seen that constructive praxis correctly classified 96% of the patients in the control group and 81% of those with moderate dementia (CDR = 2). Comparison of the control group and mild dementia group showed specificity of 71% and sensitivity of 88% ($P < 0.0001$), as presented in **Table 2**.

We had the objective of comparing the sensitivity and specificity data between MMSE and CAMCOG. The analyses performed using the CAMCOG cognitive battery showed 95% sensitivity and 93% specificity, and the cutoff point observed for this sample was 75 points (**Table 3** and **Figure 1**). The MMSE presented sensitivity of 93% and specificity of 93%, and the cutoff point was 23 points (**Table 3** and **Figure 1**).

Analyses on the ROC curve were performed only for the praxis subitems and the total praxis item (12 points). Only ideational praxis, which received 1 point for correct execution, was not assessed through the ROC curve. In relation to the constructive subitem, the cutoff point was taken to be 4 points, which had sensitivity of 69% and specificity of 98% (**Table 3** and **Figure 1**). ROC curve analysis on the ideomotor subitem presented sensitivity of 66% and specificity of 44% for a cutoff point of 4 points (**Table 3** and **Figure 1**), i.e. lower values than those of the constructive

Table 2. Accuracy of praxis instruments for levels of clinical dementia rating (CDR). CDR = 0, no dementia; CDR = 1, mild; CDR = 2, moderate

CDR	Instruments	AUC	P	95% CI	Sensitivity	Specificity	Cutoff point
0-1	Total praxis	0.82	0.0001	0.742-0.900	0.64	0.85	9
	Constructive praxis	0.88	0.00	0.808-0.946	0.88	0.71	5
	Ideomotor praxis	0.56	0.29	0.453-0.665	0.69	0.44	4
0-2	Total praxis	0.92	0.0001	0.854-0.980	0.78	0.94	8
	Constructive praxis	0.93	0.0001	0.875-0.995	0.81	0.96	3
	Ideomotor praxis	0.57	0.21	0.452-0.697	0.31	0.85	3
1-2	Total praxis	0.74	0.0001	0.623-0.856	0.59	0.79	7
	Constructive praxis	0.74	0.0001	0.624-0.863	0.56	0.88	2
	Ideomotor praxis	0.53	0.69	0.389-0.667	0.19	0.98	2

AUC = area under the curve; CI = confidence interval.

Table 3. Accuracy of different tests for diagnosing Alzheimer's disease

Instruments	AUC	P	95% CI	Sensitivity (%)	Specificity (%)	Cutoff point
CAMCOG	0.975	**< 0.0001**	94-99	95	93	75 points
MMSE	0.972	**< 0.0001**	93-99	93	93	23 points
Constructive praxis	0.905	**< 0.0001**	85-95	69	98	4 points
Total praxis	0.858	**< 0.0001**	79-90	73	84	9 points
Ideomotor praxis	0.568	0.111	49-65	66	44	4 points

AUC = area under the curve; CI = confidence interval; CAMCOG = Cambridge Cognitive Examination; MMSE = Mini-Mental State Examination. P from chi-square test.

subitem. Finally, the ROC curve methodology was performed for total praxis through CAMCOG, in order to verify this ability (by adding the scores for the three subitems: constructive, ideomotor and ideational). **Table 3** and **Figure 1** show that this presented sensitivity of 73% and specificity of 84%, with a cutoff point of 9 points.

Given that the aim of this study was to investigate sensitivity data relating to praxis and its subitems through CAMCOG, the findings demonstrated that there was a decline in Alzheimer's disease patients, particularly regarding constructive praxis.

DISCUSSION

The aim of this study was to investigate the sensitivity of praxis data from CAMCOG for evaluations on elderly people with major neurocognitive disorders. Our results showed that the mean scores for total praxis and its constructive subitem were higher among healthy elderly people, with a statistically significant difference, as shown in **Table 1**. This result can be explained by the structural brain alterations that occur in AD patients (cortical dementia with temporoparietal impairment). Involvement of the motor cortex (parietal lobe) was responsible for the alterations that were found in this evaluation. It has been reported that there is a risk that impairment of praxis skills will rapidly evolve in cases of dementia.[10,19] One hypothesis explaining the aggressive evolution of dementia in patients who present early impairment of praxis is that this may be related to degeneration of the temporal and parietal areas, i.e. the regions involved in the circuits for praxis. This hypothesis was developed through the observation that some patients evolve more slowly, while others evolve significantly faster.[13]

The statistically significant difference relating to constructive praxis may be explained by the theory that many brain regions in both hemispheres are involved in different aspects of the design copy test. This could provide an explanation for the findings of this study, through the suggestion that declines in constructive praxis are related to impairment of cognitive abilities in cases of cortical dementia, such as Alzheimer's disease.[9,26,27] The hypothesis raised from this finding is that constructive praxis provides an index for cognitive deterioration. This means that as AD progresses, it will compromise both the left and the right hemisphere diffusely.[26-28]

Analysis of praxis abilities is important in examining motor behavior, in terms of activities of daily life. The data from our study showed that praxis declined (for both total score and the constructive subitem). This may suggest that, even at mild stages of dementia, it is problematic for elderly people to continue to drive (**Table 2**). Patients at moderate stages of dementia present significant inability to deal with tasks such as driving or cooking. Driving depends on motor skills, such as praxis abilities. Driving also depends on attention, working memory and processing speed. Although only one of the skills may be impaired, management of elderly patients with major neurocognitive disorder becomes both a problem for the family and a public health problem, in that elderly drivers should be evaluated.[29] There is a need to review the praxis items within CAMCOG, so as to be able to assess the skills of elderly drivers. Impaired driving skills are only one example of

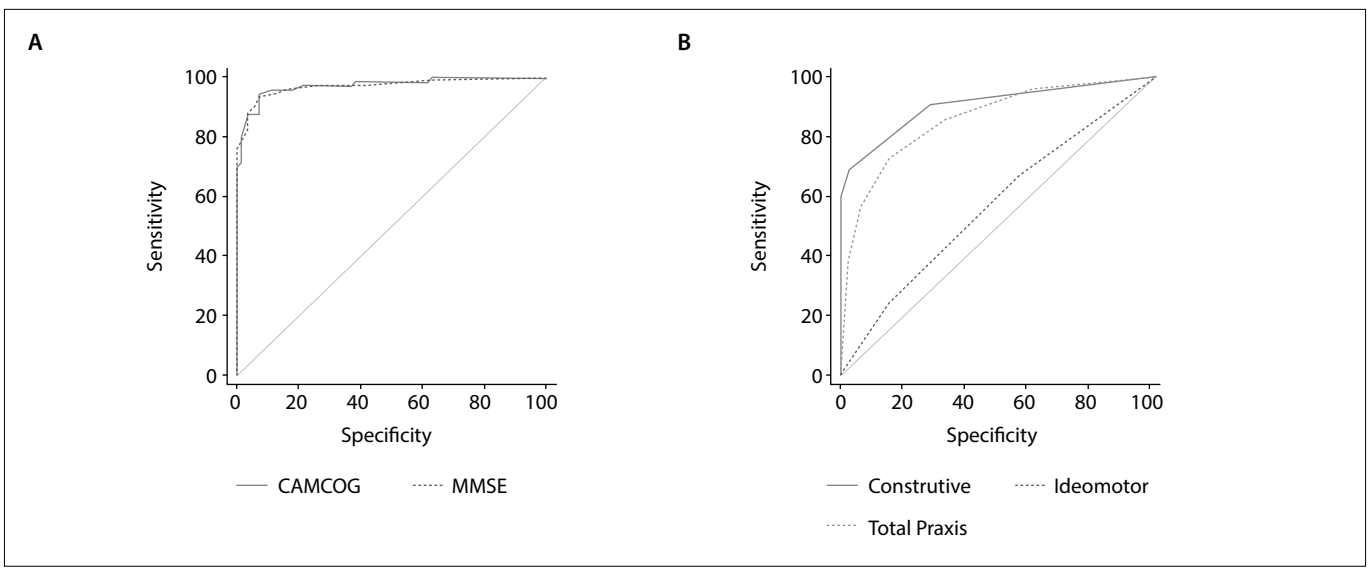

Figure 1. Graphical analysis on receiver operating characteristic (ROC) curve in relation to Cambridge Cognitive Examination (CAMCOG), Mini-Mental State Examination (MMSE), praxis and subitems. (A) Comparison of area under the curve (AUC) between MMSE and CAMCOG instruments. (B) Comparison of AUC among total praxis, constructive subitem and ideomotor subitem. Graph (B) shows that constructive praxis presents the largest value.

the negative debilitating effects of apraxia, but it is important to emphasize the general importance of evaluation of praxis, as one of the indicators of cognitive fragility among elderly patients.[30,31] Our results, presented in **Table 2**, correlated the stages of dementia (CDR) with the scores for total praxis and its constructive and ideomotor subitems. This may suggest that these items are related to stages of dementia.

Regarding constructive praxis, there is a requirement for visual skills and motor planning. Both cerebral hemispheres act towards accomplishment of constructive tasks. Errors are usually associated with right-hemisphere parietal lesions due to deficits of perception, while errors of execution are related to lesions in the left hemisphere. Ideomotor apraxia is related to lesions in the parietal cortex of the left hemisphere, in the corpus callosum and in the basal ganglia. Ideational apraxia is usually caused by severe disturbances in the temporal sequence of motor actions.[11] Assessment of constructional praxis has been extensively used in diagnostic investigations of dementia syndrome. Some tests such as the clock drawing test (CDT) and copying of pentagons are considered to be more complex because they involve organization and planning of the motor action in order to carry out the task and are also influenced by schooling level.[14] Those findings corroborate the data of the present study, which found a greater area under the curve (AUC) in the constructional subitem (AUC = 0.905) than in the total praxis item (AUC = 0.858) and the ideomotor subitem (AUC = 0.568). This explains the weak correlation between memory and praxis, since the same brain regions may not be involved in the same satisfactory performances.

Chandra et al.[13] reported that this cognitive function (ideomotor, constructive and ideational praxis) was important in relation to corticobasal degeneration (encompassing cerebral cortex and basal ganglia). In other words, from the time when neuronal loss occurs in the cortical region and basal ganglia (participating in motor circuits), patients will present impairment of intentional execution of motor tasks. There may be impairment in the early stages of dementia syndrome. Motor areas of the cortex send signals to the basal ganglia and these in turn replicate the motor signals that are transmitted to the parietal cortex. Any failure to communicate or send signals can cause apraxia.

While memory disorders tend to dominate cognitive psychology and neuropsychology, praxis deficits have been placed in the background. This often leads to difficulties in accurately interpreting the nature of motor disorders presented by patients with neurological and neuropsychiatric disorders.[24] Johnen et al.[30] and Hazan et al.[14] described these concerns in relation to aging populations and indicated that there is a need for physicians and other healthcare professionals to have access to screening tools with predictive value for identifying cognitive impairment in cases of suspected dementia. These authors stated that such instruments would need to have high diagnostic accuracy and be fast and easily administered, and that praxis tests might be able to fulfill this purpose.

Our findings demonstrated that, as screening tests, MMSE had high diagnostic efficacy (AUC = 0.972), while CAMCOG presented a satisfactory AUC = 0.975 value. Helmes[19] and Martinelli et al.[32] critically appraised the pentagon drawing test that forms part of MMSE and stated that this is an important test that evaluates organic brain dysfunction, even though it only receives a dichotomous score. These authors also stated that this test of copying a pentagon is so important for evaluating cerebral dysfunction that it should be scored independently. Our results have made us think about using the praxis item as a screening tool, because the constructive subitem (AUC = 0.905; sensitivity = 69%; specificity = 98%) was more effective in investigating cognitive impairment than was the total praxis item (AUC = 0.858; sensitivity = 73%; specificity = 84%). These findings agree with those of the studies by Hazan et al.,[14] Helmes,[19] Johnen et al.[30] and Martinelli et al.,[32] thus indicating that the most effective praxis screening tests are those that comprise constructive tasks.

Evaluation of apraxia among elderly people is a way of exploring the field of cognition as part of the diagnostic investigation of neurodegenerative diseases. It was found through the praxis subitems from CAMCOG that some patients, even those whose aging process is healthy, present some difficulties in performing such functions with accuracy.

One limitation of the present study was in relation to the severity of dementia. Moreover, we only evaluated the forms of praxis that are included in CAMCOG, which only considers three of the various types of apraxia, such as dynamic, myokinetic, gait, dressing, buccofacial, agnostic and diagnostic apraxia.

CONCLUSION

Some praxis subtests may have higher predictive diagnostic value in detecting Alzheimer's disease in mild stages. However, only constructive praxis from CAMCOG showed higher accuracy for identifying dementia. Our contribution from the present study consists of the suggestion that cognitive screening tasks consisting of constructive praxis should be used (i.e. copying of figures) and that this cognitive information could be particularly appropriate for investigating impairment in patients with suspected dementia. In addition to use of constructive praxis in screening tests, we also found that it was effective in screening for Alzheimer's disease and thus was an effective test for predominantly cortical dementia.

REFERENCES

1. Roth M, Tym E, Mountjoy C, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference

to the early detection of dementia. Br J Psychiatry. 1986;149:698-709. PMID: 3790869.

2. Bottino CMC, Almeida OP, Tamai S, et al. The Cambridge examination for mental disorders of the elderly. Tradução e adaptação para o português. Edição Brasileira. São Paulo: PROTER; 2013.
3. Aprahamian I, Martinelli JE, Cecato J, Izbicki R, Yassuda MS. Can the CAMCOG be a good cognitive test for patients with Alzheimer's disease with low levels of education? Int Psychogeriatr. 2011;23(1):96–101. PMID: 20678300; doi: 10.1017/S104161021000116X.
4. Nunes PV, Diniz BS, Radanovic M, et al. CAMcog as a screening tool for diagnosis of mild cognitive impairment and dementia in a Brazilian clinical sample of moderate to high education. Int J Geriatr Psychiatry. 2008;23(11):1127-33. PMID: 18464287; doi: 10.1002/gps.2038.
5. Paradela EM, Lopes C de S, Lourenço RA. Reliability of the Brazilian version of the Cambridge Cognitive Examination Revised CAMCOG-R. Arq Neuropsiquiatr. 2009;67(2B):439-44. PMID: 19623441.
6. Chen A, Akinyemi RO, Hase Y, et al. Frontal white matter hyperintensities, clasmatodendrosis and gliovascular abnormalities in ageing and post-stroke dementia. Brain. 2016;139(Pt1):242-58. PMID: 26667280; doi: 10.1093/brain/awv328.
7. Stephan BCM, Minett T, Muniz-Terrera G, et al. Neuropsychological profiles of vascular disease and risk of dementia: implications for defining vascular cognitive impairment no dementia (VCI-ND). Age Ageing. 2017;46(5):755-60. PMID: 28203692; doi: 10.1093/ageing/afx016.
8. Nagahama Y, Okina T, Suzuki N. Impaired imitation of gestures in mild dementia: comparison of dementia with Lewy bodies, Alzheimer's disease and vascular dementia. J Neurol Neurosurg Psychiatry. 2015;86(11):1248-52. PMID: 25515503; doi: 10.1136/jnnp-2014-309436.
9. Trojano L, Gainotti G. Drawing Disorders in Alzheimer's Disease and Other Forms of Dementia. J Alzheimer's Dis. 2016;53(1):31-52. PMID: 27104898; doi: 10.3233/JAD-160009.
10. Ward M, Cecato J, Aprahamian I, Martinelli J. Assessment for apraxia in Mild Cognitive Impairment and Alzheimer's disease. Dement Neuropsychol. 2015;9(1):71–75. PMID: 29213944; doi: 10.1590/S1980-57642015DN91000011.
11. Caixeta L. Doença de Alzheimer e suas variantes. In: Psiquiatria Geriátrica. Porto Alegre: Artmed; 2016. p. 103-31. ISBN: 9788536327020.
12. Zadikoff C, Lang A. Apraxia in movement disorders. Brain. 2005;128(Pt 7):1480-97. PMID: 15930045; doi: 10.1093/brain/awh560.
13. Chandra SR, Issac TG, Abbas MM. Apraxias in Neurodegenerative Dementias. Indian J Psychol Medicine. 2015;37(1):42-7. doi: 10.4103/0253-7176.150817.
14. Hazan E, Frankenburg F, Brenkel M, Shulman K. The test of time: a history of clock drawing. Int J Geriatr Psychiatry. 2018;33(1):e22-e30. PMID: 28556262; doi: 10.1002/gps.4731.
15. Field A. Descobrindo a estatística por meio do SPSS. Porto Alegre: Artmed; 2009. ISBN: 9788536320182.
16. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49. PMID: 7183759.
17. American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders – DSM-5; 2013.
18. McKhann G, Knopman D, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7(3):263-9. PMID: 21514250; doi: 10.1016/j.jalz.2011.03.005.
19. Helmes E. Cognitive screening of older adults: the utility of pentagon drawing. Int Psychogeriatr. 2013;25(3):413-9. PMID: 23194975; doi: 10.1017/S1041610212001998.
20. Lee S, Oh S. Visuoperceptual and constructive ability disturbances of patients with traumatic brain injury in Hutt Adaptation of the Bender Gestalt Test. Korean J Clin Psychol. 1998;17(1):311-7.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98. PMID: 1202204.
22. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982;37(3):323-9. PMID: 7069156.
23. Barbe C, Morrone I, Wolak-Thierry A, et al. Impact of functional alterations on quality of life in patients with Alzheimer's disease. Aging Ment Health. 2017;21(5):571-6. PMID: 26745259; doi: 10.1080/13607863.2015.1132674.
24. Caixeta L, Soares V, Soares CD. Avaliação cognitiva e psicolinguística do idoso. In: Caixeta L, organizador. Psiquiatria Geriátrica. Porto Alegre: Artmed; 2016. p 49-56. ISBN: 9788582712719.
25. Zuccolo P, Rzezak P, Gois JO. Praxia e Visuoconstrução. In: Malloy-Diniz LF, Fuentes D, Mattos P, organizadores. Avaliação neuropsicológica. Porto Alegre: Artmed; 2010. p. 114-22.
26. Miall RC, Nam SH, Tchalenko J. The influence of stimulus format on drawing--a functional imaging study of decision making in portrait drawing. Neuroimage. 2014;102 Pt 2:608-19. PMID: 25128710; doi: 10.1016/j.neuroimage.2014.08.015.
27. Ahn HJ, Seo SW, Chin J, et al. The cortical neuroanatomy of neuropsychological deficits in mild cognitive impairment and Alzheimer's disease: a surface-based morphometric analysis. Neuropsychologia. 2011;49(14):3931-45. PMID: 22019776; doi: 10.1016/j.neuropsychologia.2011.10.010.
28. Rizzo M, Anderson SW, Dawson J, Nawrot M. Vision and cognition in Alzheimer's disease. Neuropsychologia. 2000;38(8):1157-69. PMID: 10838150; doi: 10.1016/S0028-3932(00)00023-3.
29. Haussmann R, Buthut M, Donix M. Driving Problems in the Elderly and Cognitively Impaired. Pharmacopsychiatry. 2017;50(5):197-202. PMID: 28521367; doi: 10.1055/s-0043-109560.

30. Johnen A, Frommeyer J, Modes F, et al. Dementia apraxia test (DATE): A Brief Tool to Differentiate Behavioral Variant Frontotemporal Dementia from Alzheimer's Disease Based on Apraxia Profiles. J Alzheimer's Dis. 2016;49(3):593-605. PMID: 26484911; doi: 10.3233/JAD-150447.
31. Dedeyne L, Deschodt M, Verschueren S, Tournoy J, Gielen E. Effects of multi-domain interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic review. Clin Interv Aging. 2017;12:873-96. PMID: 28579766; doi: 10.2147/CIA.S130794.
32. Martinelli, Cecato JF, Martinelli MO, Melo BAR, Aprahamian I. Desempenho do teste do desenho do pentágono para rastreio de idosos com demência de Alzheimer [Performance of the Pentagon Drawing test for the screening of older adults with Alzheimer's dementia]. Dement Neuropsychol. 2018;12(1):54-60. doi: 10.1590/1980-57642018dn12-010008.

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Stroke at baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): a cross-sectional analysis

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KEY WORDS:
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ABSTRACT

BACKGROUND: Secondary prevention of stroke is a very important goal for achieving continuous reduction in stroke mortality rates over the next decades.

DESIGN AND SETTING: Cross-sectional analysis on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), with data from Salvador, Vitória, Belo Horizonte, Rio de Janeiro, São Paulo and Porto Alegre.

METHODS: This descriptive analysis focused on secondary prevention of stroke among participants who self-reported a medical diagnosis of stroke at the baseline of ELSA-Brasil, and its association with sociodemographic characteristics.

RESULTS: Overall, 197 participants (1.3%) reported a prior medical history of stroke. Participants with stroke were older and less educated and had lower mean monthly family income, compared with non-stroke participants. Among all stroke cases, 23.7% did not use any medication for secondary prevention of stroke. Use of secondary prevention was higher among men than among women (respectively, 59.6% versus 40.4%; P = 0.02 for aspirin; and 71.4% versus 28.6%; P = 0.04 for other antiplatelet drugs). Having private health insurance was associated with greater use of less cost-effective and more expensive medications (like angiotensinogen receptor blockers) and a tendency to use antiplatelet drugs other than aspirin, among participants reporting stroke, compared with others. Use of medication decreased as time passed after suffering a stroke.

CONCLUSIONS: In this sample of individuals with better access to healthcare services, use of secondary prevention for stroke was low, which may suggest that the situation in the general population is worse. Sex was the most important sociodemographic variable associated with low use of secondary prevention.

INTRODUCTION

Despite the declining stroke rates over recent years, with a reduction of 21% from 2005 to 2015 (19.2% to 22.8%),[1] stroke remains one of the leading causes of mortality worldwide, particularly in developing countries.[1,2] In Brazil, early mortality (at ages of less than 70 years) has presented an impressive decline since 2005, from 55.7% in that year to 30.5% in 2015, but is still very high.[3] Although the risk of death due to stroke is decreasing in all regions of Brazil, faster declines were observed in the wealthiest areas, thus exacerbating the social inequalities in the country.[4,5]

Secondary prevention of stroke mortality is a key point in relation to achieving continuous reduction in stroke mortality over the next decades. However, few studies in Brazil provide information about use of secondary prevention. In Joinville, a city in southern Brazil, out of 594 patients who were discharged from public hospitals after their first stroke, 54% did not return to a public or private hospital unit for follow-up at least twice a year; 5.7% (34/594) stated that they were not taking any secondary preventive treatment, had no intention of coming back for secondary prevention, or had no intention of taking the hospital prescription; 8.4% (50/594) looked for private care or for public healthcare units outside their health district; and 8.4% (50/594) were lost, despite thorough searching for them.[6] In another study in Pelotas (also in the southern region), the rate of use of aspirin for secondary prevention of stroke, angina pectoris and myocardial infarction was 34.3%, i.e. well below the recommended levels for prevention of cardiovascular diseases.[7]

Considering the paucity of studies evaluating secondary prevention for stroke in Brazil, we sought to conduct a cross-sectional analysis on the frequency of secondary prevention of stroke and associated sociodemographic risk factors, using data from participants who reported

having a previous medical diagnosis of stroke at the baseline examination of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

In this context, we performed a cross-sectional analysis with the main objective of evaluating secondary prevention of stroke among the participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), using self-reported information on previous stroke that was obtained at the baseline examination.

METHODS

Study design and participants

ELSA-Brasil is a cohort study on 15,105 civil servants aged 35 to 74 years living in six cities (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo and Vitória). It was designed to investigate cardiovascular diseases and diabetes and their risk factors.[8] The baseline assessment took place between August 2008 and December 2010. Previous reports presented more details about the study design, concept and sampling procedures.[8, 9-10]

In this analysis, we included all participants for whom self-reported information about stroke (N = 15,102) was available from the baseline assessment. All participants answered a question asking about a previous medical diagnosis of stroke.

Each participant was interviewed at the workplace and made a visit to the research center for clinical examinations, in accordance with standard protocols. The interviews and examinations at each site were conducted by trained personal under strict quality control.[10]

Variables

For the present analysis, the following sociodemographic variables were considered: age (years), sex, self-reported race (white, mixed race, black, Asian or indigenous), educational attainment (less than high school; high school and some tertiary education; or completed college/university or more), mean monthly family income (≤ US$ 1,245; US$ 1,246 to US$ 3,319; or ≥ US$ 3,320) and having private health insurance (%). Local currency (Brazilian reais, BRL) was converted to United States dollars (USD) at a rate of BRL 2.00 = USD 1.00 in December 2008.

Smoking and alcohol use were categorized as never, past or current.[10] Leisure-time physical activity was measured by means of the International Physical Activity Questionnaire (IPAQ), in its long form, and the subjects were classified in accordance with the World Health Organization criteria, as physically active, partly active or sedentary. Adherence to medication was assessed using simple questions asking about the frequency of use of medicines.

Anthropometric measurements were obtained using standard protocols. Body mass index was calculated as weight divided by height squared (kg/m^2). Blood pressure (BP) was taken using a validated oscillometric device, the Omron HEM 705CPINT. Three measurements were taken at one-minute intervals. The mean of the latest two BP measurements was taken to be the value for defining situations of high BP.

Presence of hypertension was defined as situations in which medications to treat hypertension were being used, or of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Presence of diabetes was defined as situations in which there was a previous medical history of diabetes, medications to treat diabetes were being used, or situations of fasting plasma glucose ≥ 126 mg/dl, two-hour plasma glucose ≥ 200 mg/dl, or HbA1C ≥ 6.5%. Presence of dyslipidemia was defined as situations in which lipid-lowering treatment was being used or of LDL-cholesterol (LDL-c) ≥ 130 mg/dl.[10] The glomerular filtration rate (GFR) was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation.

Use of medication

All participants were asked about their continuous use of prescription or non-prescription medicines and over-the-counter drugs, including pills or liquid medications. Participants were instructed to bring all their medications to the ELSA-Brasil research centers. Then, all medications taken during the last two weeks were reviewed during the baseline assessment.

The medications used were classified as antithrombotics, including anticoagulants (antivitamin K), heparin and antiplatelet medications; as different classes of antihypertensives, such as diuretics, β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensinogen receptor blockers (ARB), calcium channel blockers (CCB), vasodilators, central action and alpha-blockers; or as lipid-lowering drugs (statins and others). Medication adherence was assessed using these four questions and by asking participants to bring medications for checking in the ELSA centers (as stated above).

Conventional 12-lead electrocardiograms (ECGs) were performed using a digital device (Atria 6100, Cardiac Science Corporation, Deerfield, Wisconsin, USA) with automated readings. The technique used for carotid intima-media thickness (CIMT) measurement in ELSA-Brasil was published previously.[11] The same protocol was applied at all the sites, using a Toshiba (Aplio XG) with a 7.5 MHz linear transducer. We used MIA software to standardize the reading and interpretation of carotid scans.[12]

Statistical analysis

Cross-sectional associations with self-reported stroke, the main sociodemographic characteristics, the cerebrovascular risk factors and the use of medications for stroke secondary prevention were analyzed. Categorical variables were presented as absolute counts and proportions and were compared using the chi-square test. Continuous variables were presented as means (± standard deviation, SD) and were compared using one-way analysis of

variance (ANOVA); or as medians (with interquartile range, IQR) and were compared using the Mann-Whitney test, as necessary.

The relationships between stroke, main cerebrovascular risk factors and the use of medications for secondary prevention of stroke were tested using logistic regression models. Odds ratios (OR) with their respective 95% confidence interval (95% CI) were presented as crude ratios, as age and sex-adjusted ratios and as ratios with multivariate adjustment including age, sex, education, mean family monthly income and private health insurance.

All the analyses were performed using the Statistical Package for the Social Sciences, version 22 (SPSS Inc., Chicago, Illinois, USA). P-values < 0.05 were considered statistically significant.

Ethics statement

The ELSA-Brasil study was approved at all six centers by their institutional review boards addressing research on human participants, in accordance with the Declaration of Helsinki (approval number CEP-HU/USP: 1555/16). Written informed consent was obtained from all participants.[8]

RESULTS

Overall, 197 participants (1.3%) reported having a prior medical history of stroke. The participants with stroke were older and less educated and had lower mean monthly family income, larger waist circumference, higher systolic and diastolic blood pressure measurements and higher frequencies of hypertension, diabetes, dyslipidemia and chronic kidney disease, compared with non-stroke subjects. They reported less frequent alcohol intake than did the participants who did not report having had stroke at the baseline.

The mean CIMT values were higher among subjects who reported having had a stroke than among the other participants without this condition (**Table 1**). Except for α-blockers, which are not used for stroke participants, all classes of antihypertensive drugs were used at higher frequencies among the stroke participants than among the non-stroke participants (**Table 1**). Adherence to use of any medication was higher among the stroke participants than among the other participants: 46% among stroke participants versus 37.1% among non-stroke participants (P = 0.02). However, neither of these frequencies of use was very high.

In the bivariate analysis, the participants with stroke reported making greater use of aspirin, other antiplatelet drugs and anticoagulants (antivitamin K) (**Table 2**), compared with non-stroke participants (**Table 2**). Although there was no difference in the frequency of stroke according to sex, it was noticed that the men made greater use of aspirin (respectively, 59.6% versus 40.4%; P = 0.02) and greater use of other antiplatelet drugs (respectively, 71.4% versus 28.6%; P = 0.04), and that there was a trend towards greater use of antivitamin K drugs (respectively, 83.3% versus 16.7%; P-value = 0.056), compared with the women. Having private

Table 1. Sociodemographic and clinical characteristics and use of medication for secondary prevention, according to self-reported occurrences of stroke at the baseline examination of ELSA-Brasil

	Stroke		
	No	Yes	P-value
	n = 14,905 (%)	n = 197 (%)	
Age (years)*	52.0 ± 9.1	58.4 ± 8.9	< 0.0001
Women (%)	8,110 (54.4)	108 (54.8)	0.91
Race (%)			
White	7,700 (52.3)	88 (45.6)	
Mixed	4,143 (28.1)	59 (30.6)	
Black	2,360 (16.0)	37 (19.2)	0.41
Asian	368 (2.5)	6 (3.1)	
Indigenous	154 (1.0)	3 (1.6)	
Education (%)			
Less than high school	1,874 (12.6)	48 (24.4)	
High school and some college/university	5,162 (34.6)	69 (35.0)	< 0.0001
College/university or more	7,869 (52.8)	80 (40.6)	
Mean family monthly income in US$ (%)			
≤ 2,489.00	3,923 (26.4)	71 (36.4)	
2,490.00-6,639.00	5,648 (38.1)	60 (30.8)	0.006
≥ 6,640.00	5,269 (35.5)	64 (32.8)	
Private health insurance (%)	10,160 (68.2)	138 (70.5)	0.57
Hypertension (%)	5,268 (35.4)	132 (67.0)	< 0.0001
Controlled hypertension (%)	12,948 (86.9)	153 (77.7)	< 0.0001
Diabetes mellitus (%)	2,901 (19.5)	68 (34.5)	< 0.0001
Dyslipidemia (%)	8,647 (58)	128 (65)	0.049
Controlled dyslipidemia (%)	7,603 (51)	114 (57.9)	0.057
Chronic kidney disease (%)	943 (6.3)	33 (16.8)	< 0.0001
Atrial fibrillation or flutter (%)	48 (0.3)	0 (0)	0.42
Smoking (%)			
Never	8,495 (57.0)	99 (50.3)	
Past	4,462 (29.9)	69 (35.0)	0.16
Current	1,947 (13.1)	29 (14.7)	
Alcohol consumption (%)			
Never	1,587 (10.7)	27 (13.8)	
Past	2,973 (20.0)	61 (31.1)	< 0.0001
Current	10,320 (69.3)	108 (55.1)	
Body mass index (kg/m²)*	27.0 ± 4.8	27.1 ± 4.6	0.79
Physical activity at leisure (%)			
Inactive	9,287 (63.2)	135 (69.9)	
Partially active	1,851 (12.6)	21 (10.9)	0.15
Active	3,554 (24.2)	37 (19.2)	
CIMT* (mm)	0.92 ± 0.20	1.03 ± 0.24	< 0.0001
AAS	820 (5.5)	145 (73.6)	< 0.0001
Other antiplatelets	72 (0.5)	14 (7.1)	< 0.0001
All antiplatelets	847 (5.7)	60 (30.5)	< 0.0001
Antivitamin K	50 (0.3)	6 (3)	< 0.0001
Heparin	4 (0.0)	1 (0.5)	< 0.0001
Antihypertensives	4,383 (29.4)	134 (68)	< 0.0001
Number of antihypertensive medications			
Only 1	2,051 (13.8)	54 (27.4)	
2	1,650 (11.1)	52 (26.4)	< 0.0001
3 or more	682 (4.6)	28 (14.2)	
Diuretics	2,226 (15.0)	66 (33.5)	< 0.0001
Beta blockers	1,576 (10.6)	45 (22.8)	< 0.0001
ACEI	1,582 (10.6)	56 (28.4)	< 0.0001
ARB	1,192 (8.0)	44 (22.3)	< 0.0001
Calcium channel blockers	780 (5.2)	27 (13.7)	< 0.0001
Vasodilators	72 (0.5)	6 (3)	< 0.0001
Centrally acting antihypertensive	61 (0.4)	8 (4.1)	< 0.0001
Alpha blockers	36 (0.2)	0 (0)	0.49
Aliskiren	8 (0.1)	1 (0.5)	0.01
Cholesterol-lowering drugs	1,915 (12.9)	63 (32.0)	< 0.0001
Statins	1,764 (11.9)	59 (29.9)	< 0.0001
Controlled LDL levels	7,243 (49)	43 (42.1)	0.06
Adherence to use of any medication	37.1	46	0.02

CIMT = carotid intima-media thickness; AAS = acetylsalicylic acid, ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers. *Data are presented as means (± standard deviation).

health insurance was not associated with higher use of other antiplatelet drugs.

Table 3 shows the main classes of anti-hypertensive drugs used for stroke secondary prevention: diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensinogen receptor blockers (ARB) and calcium channel blockers (CCB). The most frequently used antihypertensive medication in the sample was diuretics, followed by ACEI, β-blockers, ARB, CCB, centrally acting hypertensives and vasodilators. No difference in the use of antihypertensive drugs was found between men and women, except

Table 2. Use of main antiplatelet and anticoagulant drugs in secondary prevention of stroke

	AAS			Other antiplatelets			Antivitamin K		
	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value
	n = 145 (%)	n = 52 (%)		n = 183 (%)	n = 14 (%)		n = 191 (%)	n = 6 (%)	
Age (years)*	58 (8.7)	59.4 (9.5)	0.37	57.9 (8.6)	64.5 (9.9)		58.2 (8.9)	64.5 (6)	0.09
Sex (%)									
Male	58 (40)	31 (59.6)	0.02	79 (43.2)	10 (71.4)	0.04	84 (44.0)	5 (83.3)	0.056
Female	87 (60)	21 (40.4)		104 (56.8)	4 (28.6)		107 (56.0)	1 (16.7)	
Race (%)									
White	60 (42.3)	28 (54.9)		80 (44.4)	8 (61.5)		84 (44.7)	4 (80.0)	
Mixed	47 (33.1)	12 (23.5)		56 (31.1)	3 (23.1)		58 (30.9)	1 (20.0)	
Black	28 (19.7)	9 (17.6)	0.58	35 (19.4)	2 (15.4)	0.78	37 (19.7)	0 (0.0)	0.60
Asian	5 (3.5)	1 (2)		6 (3.3)	0 (0)		6 (3.2)	0 (0.0)	
Indigenous	2 (1.4)	1 (2)		1 (1.7)	0 (0)		3 (1.6)	0 (0.0)	
Education (%)									
Less than high school	34 (23.4)	14 (26.9)		44 (24)	4 (28.6)		47 (24.6)	1 (16.7)	
High school and some college/university	51 (35.2)	18 (34.6)	0.87	67 (36.6)	2 (14.3)	0.23	68 (35.6)	1 (16.7)	0.41
College/university or more	60 (41.4)	20 (38.5)		72 (39.3)	8 (57.1)		76 (39.8)	4 (66.7)	
Mean monthly family income (%)									
≤ USD 1245	54 (37.8)	17 (32.7)		68 (37.4)	3 (23.1)		71 (37.6)	0 (0.0)	
USD 1246 to 3319	44 (30.8)	16 (30.8)	0.75	56 (30.8)	4 (30.8)	0.49	58 (30.7)	2 (33.3)	0.11
≥ USD 3320	45 (31.5)	19 (36.5)		58 (31.9)	6 (46.2)		60 (31.7)	4 (66.7)	
Private health insurance (%)	103 (71)	35 (67.3)	0.62	125 (68.3)	13 (92.9)	0.053	133 (69.6)	5 (83.3)	0.47

AAS = acetylsalicylic acid; USD = United States dollars.

Table 3. Main classes of antihypertensive drugs used for secondary prevention of stroke

	Diuretics		P	Beta-blockers		P	ACEI		P	ARB		P	Calcium channel blockers		P
	No	Yes		No	Yes		No	Yes		No	Yes		No	Yes	
	n = 131(%)	n = 66 (%)		n = 152 (%)	n = 45 (%)		n = 141 (%)	n = 56 (%)		n = 153 (%)	n = 44 (%)		n = 170 (%)	n = 27 (%)	
Age (years)*	57.2 (8.4)	60 (9.4)	0.009	58 (8.7)	60 (9.3)	0.22	58.3 (9.1)	58.6 (8.4)	0.81	57 (8.9)	63 (7.2)	< 0.0001	57.7 (9)	62.8 (6.9)	0.005
Sex (%)															
Female	72 (55.0)	36 (54.5)	0.96	86 (56.6)	22 (48.9)	0.36	84 (59.6)	24 (42.9)	0.03	86 (56.2)	22 (50.0)	0.47	95 (55.9)	13 (48.1)	0.45
Male	59 (45)	30 (45.5)		66 (43.4)	23 (51.1)		57 (40.4)	31 (57.1)		67 (43.8)	22 (50.0)		75 (44.1)	14 (51.9)	
Race (%)															
White	66 (52.0)	22 (33.3)		68 (45.6)	20 (45.5)		65 (47.1)	23 (41.8)		72 (48.3)	16 (36.4)		79 (47.3)	9 (34.6)	
Mixed	31 (24.4)	28 (42.4)		49 (32.9)	10 (22.7)		38 (27.5)	21 (38.2)		44 (29.5)	15 (34.1)		51 (30.5)	8 (30.8)	
Black	25 (19.7)	12 (18.2)	0.006	26 (17.4)	11 (25.0)	0.23	29 (21.0)	8 (14.5)	0.62	25 (16.8)	12 (27.3)	0.27	30 (18.0)	7 (26.9)	0.04
Asian	5 (3.9)	1 (1.5)		5 (3.4)	1 (2.3)		4 (2.9)	2 (3.6)		6 (4.0)	0 (0.0)		6 (3.6)	0 (0.0)	
Indigenous	0 (0.0)	3 (4.5)		1 (0.7)	2 (4.5)		2 (1.4)	1 (1.8)		2 (1.3)	1 (2.3)		1 (0.6)	2 (7.7)	
Education (%)															
< High school	27 (20.6)	21 (31.8)		39 (25.7)	9 (20.0)		30 (21.3)	18 (32.1)		37 (24.2)	11 (25.0)		37 (21.8)	11 (40.7)	
High school/ some college/ university	47 (35.9)	22 (33.3)	0.21	49 (32.2)	20 (44.4)	0.32	49 (34.8)	20 (35.7)	0.19	57 (37.3)	12 (27.3)	0.43	62 (36.5)	7 (25.9)	0.10
College/university or more	57 (43.5)	23 (34.8)		64 (42.1)	16 (35.6)		62 (44.0)	18 (32.1)		59 (38.6)	21 (47.7)		71 (41.8)	9 (33.3)	
Mean monthly family income (%)															
≤ USD 1245	44 (34.1)	27 (40.9)		55 (36.7)	16 (35.6)		49 (35.3)	22 (39.3)		59 (39.1)	12 (27.3)		60 (35.5)	11 (42.3)	
USD 1246 to 3319	43 (33.3)	17 (25.8)	0.50	47 (31.3)	13 (28.9)	0.90	41 (29.5)	19 (33.9)	0.52	47 (31.1)	13 (29.5)	0.20	52 (30.8)	8 (30.8)	0.74
≥ USD 3320	42 (32.6)	22 (33.3)		48 (32.0)	16 (35.6)		49 (35.3)	15 (26.8)		45 (29.8)	19 (43.2)		57 (33.7)	7 (26.9)	
Private health insurance (%)	97 (74.0)	41 (62.1)	0.09	105 (69.1)	33 (73.3)	0.58	107 (77.9)	31 (55.4)	0.005	100 (65.4)	38 (86.4)	0.007	120 (70.6)	18 (66.7)	0.68

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers.

for ACEI, for which there was greater use among men than among woman (57.1% versus 42.9%; P-value = 0.03).

Lower frequency of diuretic use was observed among whites with stroke and higher frequency of diuretic use was observed among mixed-race participants with stroke, compared with others (P = 0.006). Furthermore, lower frequency of CCB use was noticed among whites with stroke and higher frequency of CCB use among black participants with stroke, compared with others without this condition (P = 0.04).

Regarding educational attainment, use of centrally acting antihypertensive medication was higher among stroke participants with less education than among participants with higher levels of education. Having private health insurance was associated with higher use of ARB among stroke participants, compared with others.

Use of statins was also greater among older participants (P < 0.0001) and among men in comparison with women (64.4% versus 35.6%; P < 0.0001). Stroke participants reported making greater use of statins, compared with non-stroke participants. The frequency of use of statins was higher among white participants with stroke, compared with others (P = 0.04) (**Table 4**).

Table 5 shows the use of medication according to the time that had elapsed since the stroke. Absence of use of medication increased with increasing length of time since the stroke, such that around 20% of the participants for whom 10 years or less had elapsed since their stroke were not using medication and around 30% of the participants who reported that 11 years or more had elapsed since their stroke were not using medication. Overall, the use of medication for secondary stroke prevention was very low in this sample and it declined with increasing length of time since the stroke. The percentage of the participants who reported using at least one antiplatelet or anticoagulant drug in association with antihypertensives and statins was around 15% to 20%.

Table 4. Characteristics of participants with stroke according to use of statins

	Use of statins		
	No	Yes	P-value
	n = 138 (%)	n = 59 (%)	
Age (years)*	56.7 (8.7)	62.3 (8.2)	< 0.0001
Sex (%)			
Male	51 (37.0)	38 (64.4)	< 0.0001
Female	87 (63.0)	21 (35.6)	
Race (%)			
White	54 (39.7)	34 (59.6)	
Mixed race	45 (33.1)	14 (24.6)	
Black	31 (22.8)	6 (10.5)	0.04
Asian	3 (2.2)	3 (5.3)	
Indigenous	3 (2.2)	0 (0.0)	
Years of education (%)			
< 9	35 (25.4)	13 (22.0)	
9-11	51 (37.0)	18 (30.5)	0.44
> 11	52 (37.7)	28 (47.5)	
Mean family monthly income (%)			
≤ USD 1245	55 (40.1)	16 (27.6)	
USD 1246 to 3319	43 (31.4)	17 (29.3)	0.11
≥ USD 3320	39 (28.5)	25 (43.1)	
Private health insurance (%)			
No	44 (31.9)	15 (25.4)	0.37
Yes	94 (68.1)	44 (74.6)	

DISCUSSION

Overall, the use of medication was very low among these participants in ELSA-Brasil, despite the existence of cheap medications such as aspirin or β-blockers, and a national policy that guarantees access to essential medications for all citizens.

Although the frequencies of stroke according to sex were similar (no statistical difference), the men reported making greater use of medication for secondary prevention of stroke than did women. Recent data on the prevalence of stroke from the National Health Survey (Pesquisa Nacional de Saúde, PNS) and from the Global Burden of Disease Brasil study have also shown similar results.[3,6] If the prevalence is similar between the sexes, and considering that women use healthcare services more frequently than men do,[14-16] it might have been expected that women would have higher use of medication than men.

The data from ELSA-Brasil showed that the prevalence rates regarding awareness about being hypertensive, use of medication and control of high blood pressure were higher among women than among men. The same was true for use of statins. One possible explanation is that participants who reported having had a stroke presented lower mean monthly family income than did non-stroke participants. Moreover, from analysis on the data according to sex, it could be seen that women who reported having had a stroke presented lower income than did men who reported having had a stroke. Discussion of adherence to treatment is also a complex matter since it is likely that some participants, especially women, had not had any treatment prescribed and thus were not taking any medication. Therefore, our results are similar to those from a previous Brazilian study that reported that there was only low use of medication for chronic diseases.[17]

Our data highlighted some important points. ELSA-Brasil participants are civil servants with higher levels of education, higher mean monthly family income and better access to medical services, compared with the general Brazilian population. However, even considering this better access to medical services, the frequency at which participants who had had a stroke reported using antiplatelet or anticoagulant drugs in association with antihypertensives and statins was never higher than 21%. Nonuse of medication was less than 20% among individuals who had had a stroke ten years or less before their baseline interview, but this rose to more than 30% among those whose stroke was more than 10 years earlier. Frequency of use of medication also declined according to the length of time since the stroke.

Brazil has implemented a national drug policy to guarantee access to essential drugs for all citizens.[18] Drugs used for secondary prevention of stroke are in the list of essential drug products (RENAME).[19] The Ministry of Health has also created the Brazilian Popular Pharmacy Program (FPB)[20] with the aim of increasing access to essential and primary medicines for all citizens.[21,22]

Although these drugs should be available for all individuals, some studies have indicated that not all antiplatelet or antihypertensive medications are always available through public healthcare system.[23,24] It is important to note that at the time of the baseline examinations in ELSA-Brasil (between August 2008 and December 2010) only two antihypertensive medications were included in the Popular Pharmacy Program: beta blockers and ACEI. In 2010, statins and ARB were also included, and aspirin was added in 2011. Although our data did not show any difference in the use of secondary prevention according to mean monthly family income, it would be interesting to investigate the extent to which secondary prevention was being used at the time of the second ELSA-Brasil examination (conducted between 2012 and 2014). At that time, all the drugs used for prevention were available through all programs.

The pattern of statin use that we observed is similar to that presented in the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS). Data from that study showed that the use of medication was highest among white men followed by the levels among black men, white women and black women.[25] One potential explanation for the more aggressive use of statins among white men relative to the other groups may lie in physicians' treatment patterns and habits.[25] In 2004, Mosca et al. found that although primary care physicians widely supported the National Cholesterol Education Program's Third Adult Treatment Panel guidelines and coronary heart disease (CHD) risk stratification, less than half of these physicians implemented risk calculation tools in their clinical practice. This resulted in consistent underestimation of CHD risk, especially among women.[26]

Having private health insurance was associated with higher frequency of ARB prescription than of ACEI prescription and a borderline trend towards use of antiplatelet drugs other than aspirin, along with higher frequency of use of centrally acting antihypertensive drugs. These data suggest that participants with private health insurance are using less cost-effective and more expensive antihypertensive and antiplatelet medications, in comparison with participants without private health insurance. Although no information regarding the incidence of the main stroke subtypes (ischemic or hemorrhagic) was available from ELSA-Brasil, no participant who self-reported having had a stroke in this sample presented atrial fibrillation or flutter. This may explain the low use of anticoagulants in the sample.

Stroke is a preventable disease. There is now a growing body of evidence highlighting the importance of comprehensive risk factor management for improving survival among stroke participants, especially through detection, treatment and control of high blood pressure.[27] Despite the good results from hypertension treatment that were achieved in one selected sample,[28] a recent meta-analysis based on ten Brazilian cross-sectional studies[29] estimated that in Brazil in the 2000s, only 24.1% of the cases of high blood pressure were kept under control. Although this percentage was comparable to that of other countries,[30-32] it was still low.

Some authors have adopted the concept of epidemiological transition to describe trends among cardiovascular diseases. Briefly, there was firstly a shift from rheumatic heart disease to hypertensive disease and hemorrhagic stroke. In the next stage, there was a shift from hemorrhagic to ischemic stroke, and finally to CHD among middle-aged individuals. In the last stage, there was a switch from stroke to CHD mortality.[32] Brazil is in the last stage

Table 5. Medication use according to drug classes and length of time since occurrence of stroke, among participants with self-reported stroke

Drug classes and combinations	Time since stroke (years)				Total
	n (%)				
	< 5	5-10	11-15	> 15	
No medication use	14 (19.4)	8 (16.7)	11 (35.5)	12 (30.8)	45 (23.7)
Only aspirin	3 (4.2)	2 (4.2)	2 (6.5)	0 (0)	7 (3.7)
Only antihypertensives	17 (23.6)	22 (45.8)	10 (32.3)	14 (33.3)	63 (33.2)
Only statins	3 (4.2)	0 (0)	1 (3.2)	3 (25.8)	7 (3.7)
Aspirin and any antihypertensive	9 (12.5)	3 (6.3)	2 (6.5)	2 (7.7)	16 (2)
Aspirin and statins	2 (2.8)	0 (0)	0 (0)	0 (0)	2 (1.1)
Other antiplatelets and antihypertensives	2 (2.8)	0 (0)	0 (0)	0 (0)	2 (1.1)
Aspirin, other antiplatelets and statins	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (1.1)
Antihypertensives and statins	7 (9.7)	5 (10.4)	1 (3.2)	1 (2.6)	14 (7.4)
Aspirin, antihypertensives and statins	12 (16.7)	3 (6.3)	2 (6.5)	3 (7.7)	19 (10.5)
Antivitamin K, antihypertensives and statins	1 (1.4)	1 (2.1)	1 (3.2)	0 (0)	3 (1.6)
Other antiplatelets, antihypertensives and statins	1 (1.4)	0 (0)	0 (0)	3 (7.7)	4 (2.1)
AAS, antiplatelets, antihypertensives and statins	1 (1.4)	3 (6.3)	1 (3.3)	1 (2.6)	6 (3.2)
Total	**72**	**48**	**31**	**39**	**190**

of this epidemiological transition. Around ten years ago (2007), ischemic heart diseases surpassed stroke as the most prevalent cause of death in this country. However, the burden of stroke is still very high and is associated with premature death.

In this sample from ELSA-Brasil, which had better access to healthcare and higher monthly income than that of the general population of Brazil, the frequency of use of secondary prevention was very low. This finding reaffirms that stroke is still a neglected disease in Brazil,[34] and that this scenario has not changed over the last 10 years.[33,34]

This study had several limitations. The most important of these was that information about stroke in the baseline examination was self-reported, based on reports of previous medical diagnoses of stroke. Therefore, there was no information either about the frequency of the main subtypes of stroke (ischemic and hemorrhagic) or any confirmation of the diagnosis of stroke through medical records or imaging.

Recently, a study calculated the specificity of self-reported diagnoses of stroke using hospital data as the gold standard. It reported values of around 99%, but with low sensitivity.[35] In epidemiological studies, it is preferred to use questionnaires with greater specificity than sensitivity. Thus, in our study, self-reported occurrences of stroke were most likely true cases. However, milder cases that might have corresponded to minor stroke were likely to have remained undiagnosed as stroke. Thus, such cases would not be reported by ELSA-Brasil participants and, consequently, they are not included in this analysis. Therefore, it is still possible that there may have been some misclassification of cases of stroke in our study.

Interestingly, higher frequencies of risk factors and higher CIMT values were found among stroke participants than among other individuals without this condition, thus suggesting that the self-reported information indeed had value. Furthermore, detailed information about the participants' use of medication was available, and this provided an insight into the situation of secondary prevention of stroke in this sample. However, we did not have access to the medical reasons for prescribing specific medications to specific patients. Moreover, the eligibility criteria for ELSA-Brasil excluded individuals with communication problems or with cognitive deficits, which probably excluded some stroke cases. Hence, cases of stroke in ELSA-Brasil were probably milder cases with less incapacity than what has been seen in other samples.

Discussion of adherence to treatment is also a complex matter since it is likely that some participants, especially women, had not been prescribed any treatment and thus were not taking any medication. Thus, our results are similar to those of a previous Brazilian study that reported low use of medications for chronic diseases.[17] Considering that the ELSA-Brasil sample had a higher educational level, higher mean monthly family income and better access to healthcare services, the overall picture for the general population in Brazil is probably worse.

CONCLUSIONS

In the ELSA-Brasil, the frequency of use of secondary prevention for stroke was low and decreased as the length of time since the stroke increased. Moreover, sex was the variable most associated with use of secondary prevention in this sample. Men reported greater use of medication for secondary prevention of stroke than women, thus suggesting that the rate of prescription of medications for secondary prevention of stroke was low among woman.

REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544. PMID: 27733281; doi: 10.1016/S0140-6736(16)31012-1.
2. Feigin VL, Mensah GA, Norrving B, et al. Atlas of the Global Burden of Stroke (1990-2013): The GBD 2013 Study. Neuroepidemiology. 2015;45(3):230-6. PMID: 26505985; doi: 10.1159/000441106.
3. Lotufo PA, Goulart AC, Passos VMA, et al. Cerebrovascular disease in Brazil from 1990 to 2015: Global Burden of Disease 2015. Rev Bras Epidemiol. 2017;20Suppl 01(Suppl 01):129-41. PMID: 28658378; doi: 10.1590/1980-5497201700050011.
4. Lotufo PA, Goulart AC, Fernandes TG, Benseñor IM. A reappraisal of stroke mortality trends in Brazil (1979-2009). Int J Stroke. 2013;8(3):155-63. PMID: 22297034; doi: 10.1111/j.1747-4949.2011.00757.x.
5. Fernandes TG, Bando DH, Alencar AP, Benseñor IM, Lotufo PA. Income inequalities and stroke mortality trends in Sao Paulo, Brazil, 1996-2011. São Paulo Med J. 2015;133(6):4579. PMID: 26044779; doi: 10.1111/ijs.12526.
6. Cabral NL, Franco S, Longo A, et al. The Brazilian Family Health Program and secondary stroke and myocardial infarction prevention: a 6-year cohort study. Am J Public Health. 2012;102(12):e90-5. PMID: 23078478; doi: 10.2105/AJPH.2012.301024.
7. Vianna CA, González DA, Matijasevich A. Utilização de ácido acetilsalicílico (AAS) na prevenção de doenças cardiovasculares: um estudo de base populacional [Aspirin use in cardiovascular disease prevention: a population-based study]. Cad Saúde Pública. 2012;28(6):1122-32. PMID: 22666816; doi: 10.1590/S0102-311X2012000600011.
8. Aquino EM, Barreto SM, Benseñor IM, et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol. 2012;175(4):315-24. PMID: 22234482; doi: 10.1093/aje/kwr294.
9. Schmidt MI, Duncan BB, Mill JG, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75. PMID: 24585730; doi: 10.1093/ije/dyu027.
10. Benseñor IM, Griep RH, Pinto KA, et al. Rotinas de organização de exames e entrevistas no centro de investigação ELSA-Brasil [Routines of organization of clinical tests and interviews in the ELSA-Brasil investigation center]. Rev Saúde Pública. 2013;47 (suppl 2):37-47. PMID: 24346719; doi: 10.1590/S0034-8910.2013047003780.

11. Mill JG, Pinto K, Griep RH, et al. Aferições e exames clínicos realizados nos participantes do ELSA-Brasil [Medical assessments and measurements in ELSA-Brasil]. Rev Saúde Pública. 2013;47(Suppl 2):54-62. PMID: 24346721; doi: 10.1590/S0034-8910.2013047003851.
12. Santos IS, Bittencourt MS, Oliveira IR, et al. Carotid intima-media thickness value distributions in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Atherosclerosis. 2014;237(1):227-35. PMID: 25244507; doi: 10.1016/j.atherosclerosis.2014.09.004.
14. Stoverinck MJ, Lagro-Janssen AL, Weel CV. Sex differences in health problems, diagnostic testing, and referral in primary care. J Fam Pract. 1996;43(6):567-76. PMID: 8969705.
15. Koutis AD, Isacsson A, Lindholm LH, et al. Use of primary health care in Spili, Crete, and in Dalby, Sweden. Scand J Prim Health Care. 1991;9(4):297-302. PMID: 1792458.
16. Aquino EM, Menezes GM, Amoedo MB. Gênero e saúde no Brasil: considerações a partir da Pesquisa Nacional por Amostra de Domicílios [Gender and health in Brazil: considerations based on the National Household Sampling Survey]. Rev Saúde Pública. 1992;26(3):195-202. PMID: 1342501; doi: 10.1590/S0034-89101992000300011.
17. Bermudez JA, Barros MB. Perfil do acesso e da utilização de medicamentos da população brasileira – contribuições e desafios da PNAUM – Inquérito Domiciliar [Profile of access and use of medicines in the Brazilian population – contributions and challenges of PNAUM – Household Survey]. Rev Saúde Pública. 2016;50(suppl 2):2s. PMID: 27982385; doi: 10.1590/s1518-8787.201605000supl2ap.
18. Brasil. Portaria no 3.916. Diário Oficial da União 1998 novembro 10:18 (s. 1, n. 215-E). Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/1998/prt3916_30_10_1998.html. Accessed in 2018 (Jun 11).
19. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Assistência Farmacêutica e Insumos Estratégicos. Relação Nacional de Medicamentos Essenciais: RENAME 2014 / Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Assistência Farmacêutica e Insumos Estratégicos. – 9. ed. rev. e atual. – Brasília: Ministério da Saúde, 2015.
20. Brasil. Ministério da Saúde, Fundação Oswaldo Cruz. Programa Farmácia Popular do Brasil: manual básico/Ministério da Saúde, Fundação Oswaldo Cruz. Brasília: Editora do Ministério da Saúde; 2005. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/PROGRAMA_FARMACIA_POPULAR.pdf. Accessed in 2018 (Jun 11).
21. Yamauti SM, Barberato-Filho S, Lopes LC. Elenco de medicamentos do Programa Farmácia Popular do Brasil e a Política de Nacional Assistência Farmacêutica [The list of drugs in the Popular Pharmacy Program and the Brazilian National Pharmaceutical Care Policy]. Cad Saúde Pública. 2015;31(8):1648-62. PMID: 26375644; doi: 10.1590/0102-311X00054814.
22. Pinto C du B, Miranda ES, Emmerick IC, Costa N do R, Castro CG. Preços e disponibilidade de medicamentos no Programa Farmácia Popular do Brasil [Medicine prices and availability in the Brazilian Popular Pharmacy Program]. Rev Saúde Pública. 2010;44(4):611-9. PMID: 20585741; doi: 10.1590/S0034-89102010005000021.
23. Guerra AA Jr, Acúrcio F de A, Gomes CA, et al. Disponibilidad de medicamentos esenciales en dos regiones de Minas Gerais, Brasil [Availability of essential drugs in two regions of Minas Gerais, Brazil]. Rev Panam Salud Publica. 2004;15(3):168-75. PMID: 15096289.
24. Dal Pizzol T da S, Trevisol DJ, Heineck I, et al. Adesão a listas de medicamentos essenciais em municípios de três estados brasileiros [Adherence to essential medicines in cities from three Brazilian states]. Cad Saúde Pública. 2010;26(4):827-36. PMID: 20512222; doi: 10.1590/S0102-311X2010000400024.
25. Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-Sex Differences in Statin Use and Low-Density Lipoprotein Cholesterol Control Among People with Diabetes Mellitus in the Reasons for Geographic and Racial Differences in Stroke Study. J Am Heart Assoc. 2017;6(5). pii: e004264. PMID: 28490523; doi: 10.1161/JAHA.116.004264.
26. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation. 2005;111(4):499–510. PMID: 15687140; doi: 10.1161/01.CIR.0000154568.43333.82.
27. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160-236. PMID: 24788967; doi: 10.1161/STR.0000000000000024.
28. Chor D, Pinho Ribeiro AL, Sá Carvalho M, et al. Prevalence, Awareness, Treatment and Influence of Socioeconomic Variables on Control of High Blood Pressure: Results of the ELSA-Brasil Study. PLoS One. 2015;10(6):e0127382. PMID: 26102079; doi: 10.1371/journal.pone.0127382.
29. Picon RV, Fuchs FD, Moreira LB, Riegel G, Fuchs SC. Trends in prevalence of hypertension in Brazil: a systematic review with meta-analysis. PLoS ONE. 2012;7(10):e48255. PMID: 23118964; doi: 10.1371/journal.pone.0048255.
30. Carrington MJ, Jennings GL, Stewart S. Pressure points in primary care: blood pressure and management of hypertension in 532050 patients from 2005 to 2010. J Hypertens. 2013;31(6):1265-71. PMID: 23552128; doi: 10.1097/HJH.0b013e3283606bc7.
31. Fasce E, Campos I, Ibáñez P, et al. Trends in prevalence, awareness, treatment and control of hypertension in urban communities in Chile. J Hypertens. 2007;25(9):1807-11. PMID: 17762644; doi: 10.1097/HJH.0b013e328244e481.
32. Guo F, He D, Zhang W, Walton RG. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. J Am Coll Cardiol. 2012;60(7):599-606. PMID: 22796254; doi: 10.1016/j.jacc.2012.04.026.
33. Lotufo PA, Benseñor IM. Stroke mortality in Brazil: one example of delayed epidemiological cardiovascular transition. Int J Stroke. 2009;4(1):40-1. PMID: 19236497; doi: 10.1111/j.1747-4949.2009.00240.x.
34. Lotufo PA. Stroke is still a neglected disease in Brazil. Sao Paulo Med J. 2015;133(6):457-9. PMID: 26760122; doi: 10.1590/1516-3180.2015.13360510.

35. Kim YY, Park JH, Kang HJ, et al. Level of Agreement and Factors Associated With Discrepancies Between Nationwide Medical History Questionnaires and Hospital Claims Data. J Prev Med Public Health. 2017;50(5):294-302. PMID: 29020761; doi: 10.3961/jpmph.17.024.

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Use of antibiotics by adults: a population-based cross-sectional study

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ABSTRACT

BACKGROUND: The consumption of antibiotics has been widely discussed, mainly because of antibacterial resistance, which has become a worldwide concern. In Brazil, sale of antibiotics is currently ruled by Agência Nacional de Vigilância Sanitária (ANVISA) regulation RDC 20/2011, which restricts sales to those made under medical prescription. The aims of this study were to evaluate antibiotic use and associated factors among adults in the Metropolitan Region of Manaus, Amazonas, Brazil, and to assess the proportion of self-medication from this use.

DESIGN AND SETTING: Population-based cross-sectional study conducted in the Metropolitan Region of Manaus between May and August 2015.

METHODS: Adults aged ≥ 18 years were selected through probabilistic sampling in three stages. Trained interviewers collected data from the participants in their homes. Antibiotic consumption over the last 15 days was reported. Bivariate analysis was used to calculate the prevalence ratio (PR) of antibiotic usage, with 95% confidence interval (95% CI). A multivariate model adjusted according to significant variables at $P \leq 0.20$ using Poisson regression with robust variance was constructed.

RESULTS: The prevalence of antibiotic use was 3.4% (95% CI 2.8-4.0%). Adjusted analysis showed that consumption was higher among women than among men (PR 1.58; 95% CI 1.11-2.24) and among people with fair health status than among those with good health (PR 1.52; 95% CI 1.08-2.15). The prevalence of self-medication was 19.0%; amoxicillin was the most self-medicated antibiotic (10/26).

CONCLUSION: Antibiotic use was associated with women and individuals with fair health status. One fifth of the antibiotics were consumed through self-medication, contrary to the current Brazilian legislation.

INTRODUCTION

Antimicrobials are medicines that kill or prevent the growth of pathological microorganisms in the body. Among antimicrobial agents, antibiotics are among the most common drugs used worldwide.[1] Antibiotic therapy is intended for treatment of potential or proven bacterial infections. Administration of antibiotics consists of a set of actions that aims to optimize their use, through choosing the most appropriate medicine for a particular treatment and its dosage, route and time of administration, as well as minimizing undesirable events, such as toxicity and bacterial resistance.[2,3] This makes it very important to analyze the profile of the population exposed to these agents, since their action may be affected by gender, age and other factors.

Use of antimicrobials is associated with the threat of antimicrobial resistance. Different sources and transmission routes influence antimicrobial resistance, including healthcare, agriculture and the natural environment.[4] It has been estimated conservatively that 700,000 deaths per year occur consequently to antimicrobial resistance and that by 2050, there might be 10 million deaths per year. Consequently, there will be economic losses of 100 trillion dollars due to resistant infections worldwide, if the current scenario does not change.[5] In Brazil, sale of antibiotics has been regulated since 2010, initially through resolution (Resolução de Diretoria Colegiada, RDC) number 44/2010 of the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA), and subsequently through ANVISA resolution RDC 20/2011, which remains in force. RDC 20/2011 specifies that the sale is only authorized upon presentation of two copies of a medical prescription valid for 10 days, of which one will be kept by the pharmacist.[6]

Despite the requirement for a medical prescription, self-medication is often reported. A population-based cross-sectional study conducted in the state of Goiás in 2008 observed that 7% of the interviewees used antibiotics in the month prior to the interview, and that 9% of this usage

occurred without prescription.[7] In addition, use for a longer or shorter time than indicated was common, thus potentially contributing towards bacterial resistance.

No population-based studies evaluating the consumption of antibiotics after their use became regulated in Brazil are available. Assessment of the consumption of these products by the population and the proportion of nonprescription use is important for measuring the extent of exposure and the effect of the legislation on people's health.

OBJECTIVE

The purpose of this study was to evaluate the prevalence of antibiotic consumption and associated factors among adults in a metropolitan region in northern Brazil, and to estimate the rate of self-medication.

METHODS

Design

This was a population-based cross-sectional study conducted between May and August 2015 among adults living in the Metropolitan Region of Manaus, which is located in the northern region of Brazil. This study formed part of a larger research project that aimed to evaluate the use of healthcare inputs and services.[8]

Setting

The Metropolitan Region of Manaus is composed of the capital of the state of Amazonas (Manaus), and seven other municipalities: Careiro da Várzea, Iranduba, Manacapuru, Itacoatiara, Novo Airão, Presidente Figueiredo and Rio Preto da Eva. In 2010, this region had over 2.1 million inhabitants, i.e. more than 60% of the population of Amazonas. In 2010, this region occupied 19th position in the Brazilian ranking of the Municipal Human Development Index (Índice de Desenvolvimento Humano Municipal, IDHM), out of a total of 20 metropolitan regions in Brazil, among which São Paulo was in first position.[9]

Participants and sample size

Adults of at least 18 years of age who were living in the region were eligible for inclusion. We calculated the sample size as 4,000 adults to be interviewed, through considering the following factors: 2,106,322 adults living in the region, 50% healthcare service utilization rate, 95% confidence level, 2% accuracy and design effect of 1.5, with an addition of 10% to compensate for losses.[8]

The participants were selected by means of probabilistic sampling in three stages. From 2,647 urban census tracts, 400 primary and 20 secondary census tracts were selected through probabilistic sampling. The households were selected by means of systematic sampling: the first household was drawn and, from this, every 20th house in the same street was systematically visited. In cases of refusal or unavailability, the house immediately to the right was visited, and the same process was repeated to the left, if necessary. The third step was to select the participant to be interviewed: all adults present in the house were registered and one was drawn in accordance with pre-defined age and sex quotas, so as to reach population representativeness.

Variables, data sources and measurement

The data were collected in the participants' homes by 14 trained interviewers using electronic devices, after each participant had agreed to participate in the survey by signing an informed consent form.

The primary outcome was the use of antibiotics over the last 15 days. The independent variables included: sex (female or male); age (in years); social class according to the Brazilian Economic Classification Criteria (A, B, C or D/E), which is based on the number of household appliances, number of domestic employees, level of education of the head of the family and access to urban services;[10] self-assessment of health status (good, fair or poor); and use of healthcare services over the last 15 days (yes or no).

The use of medicines over the previous 15 days was measured using the question *"Over the past 15 days (or two weeks) did you take any medicine?"*. In cases of a positive response, the name of the medicine, the disease or health problem, the length of time for which the medicine was used, the person responsible for indication and the form of acquisition of the medicine were recorded as reported by the interviewee. After the data had been tabulated, the names of the medicines were surveyed in accordance with the Brazilian list of common names and were then classified using the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization.[11] Medicines that remained unidentified, either due to an indecipherable name or due to not being listed in the ATC were classified as "non-codifiable".

The indication and source of acquisition of the antibiotic was measured by the question: *"Who prescribed it?"* (physician, sales clerk, relatives/neighbors, interviewee upon his/her own account, pharmacist or other) and *"What was the form of acquisition of the medicine?"* (health insurance, *Farmácia Popular* (public co-payment program), public healthcare system, drug store or other). A situation of self-medication was recorded when the person responsible for antibiotic indication was not a physician.

After the data had been tabulated, interviews in which use of antibiotics was reported were identified in the database in accordance with the list of medicines included in ANVISA regulation RDC 20/2011. These products corresponded to the antimicrobials that are included in group J of the ATC, i.e. antiinfectives for systemic use; specifically, in the groups J01 (J01A tetracyclines, J01B amphenicols,

J01C beta-lactam antibacterials, penicillins, J01D other beta-lactam antibacterials, J01E sulfonamides and trimethoprim, J01F macrolides, lincosamides and streptogramins, J01G aminoglycoside antibacterials, J01M quinolone antibacterials, J01X other antibacterials) and J04 (antimycobacterials: J04A drugs for treatment of tuberculosis and J04B drugs for treatment of leprosy).[11]

Statistical methods

Initially, descriptive statistics were obtained from the variables of the study, and the absolute and relative frequencies of each variable and the frequency of antibiotic use per variable were calculated. Poisson regression with robust variance was performed to calculate the prevalence ratios (PR) of antibiotic use, with the 95% confidence interval (95% CI). Firstly, we performed bivariate analysis: the variables that were significant at the level $P \leq 0.20$ were included in the multivariate model to calculate adjusted PRs. Associations were considered significant if $P < 0.05$. The Wald test was used to calculate the P-values of the variables. The analyses were performed using the Stata 14.2 software, taking into account the complex sampling design (svy command).

Ethics

The Research Ethics Committee of the Federal University of Amazonas (Universidade Federal do Amazonas, UFAM) approved the project, through report no. 974,428 of March 3, 2015 (certificate of presentation for ethics assessment on the Brazil Platform [CAAE] 42203615.4.0000.5020).

RESULTS

The survey included 4,001 adults, of whom 136 reported consuming antibiotics, at the rate of one antibiotic per person. Thus, the prevalence of antibiotic consumption over the 15 days prior to the interview was 3.4% (95% CI: 2.8-4.0%).

The study population showed slight predominance of women (52.8%) and individuals between 25 and 34 years of age (28.8%), who were in economic class C (57.1%), who had completed high school (47.5%), who were in good health (66.1%) and who had not used any healthcare services over the 15 days prior to the interview (79.0%).

The frequency of use was higher among women (4.2%) than among men (2.5%), and among adults aged 25 to 34 (3.8%) and 35 to 44 (3.7%), while use was less frequent among the elderly (2.8%). Consumption was higher among the poorest population (D/E, 4.1%), and among individuals who reported having fair health (4.6%), as shown in **Table 1**.

In the bivariate analysis (**Table 2**), higher consumption of antibiotics was observed among women (PR 1.70; 95% CI 1.20-2.40), people with fair health (PR 1.63; 95% CI 1.15-2.32) and people in social class D/E (PR 1.71; 95% CI 0.96-3.05).

In the multivariate analysis, which was adjusted according to sex, health status and social class, use of antibiotics were higher among women than among men (PR 1.58; 95% CI 1.11-2.24) and among people with fair health status in comparison with good health status (PR 0.52; 95% CI 1.08-2.15). No association was found between antibiotic consumption and age, social class, education level or use of healthcare services over the previous 15 days.

Among the 136 people who used an antibiotic, a medical prescription was the main form of indication (81.0%; **Table 3**), while 19% used an antibiotic through self-medication, without a medical prescription. Use upon the interviewee's own account totaled 13.2%, while use upon suggestion from relatives and neighbors comprised 5.1% and from a pharmacist, 0.7%. Purchases of antibiotics without a prescription were self-reported. No further investigation was made about how the individuals could purchase the medication without a physician prescription. Cephalexin (39.7%) and amoxicillin (29.4%) were the drugs most used, followed by benzathine benzylpenicillin (4.4%), ciprofloxacin (3.7%), sulfadiazine (3.7%), tetracycline (3.7%), azithromycin (2.9%) and levofloxacin (2.9%). There were 10 cases of self-medication with amoxicillin,

Table 1. Main characteristics of the population and frequency of antibiotic consumption, adjusted for the complex sampling design. Metropolitan Region of Manaus, 2015 (n = 4,001)

Characteristics	Population		Antibiotic consumption	
	n	%	n	%
Sex				
Male	1,888	47.2	47	2.5
Female	2,133	52.8	89	4.2
Age (years)				
18-24	838	20.9	28	3.4
25-34	1,152	28.8	44	3.8
35-44	843	21.1	31	3.7
45-59	772	19.3	22	2.9
60 and over	396	9.9	11	2.8
Social class				
A/B	269	15.7	15	2.4
C	2,285	57.1	77	3.4
D/E	1,087	27.1	44	4.1
Education				
Higher education or above	158	4.0	7	2.5
High school	1,903	47.5	74	3.9
Elementary school	649	16.2	14	2.6
Less than elementary school	1,291	32.3	41	3.2
Health status				
Good	2,646	66.1	75	2.8
Fair	1,108	27.7	15	4.6
Poor	247	6.2	10	4.0
Healthcare service use over the last 15 days				
Did not use	3,163	79.0	104	3.3
Used	838	21.0	32	3.8

six with cephalexin and four with tetracycline, which are the antibiotics most commonly consumed without medical prescription. There were also three cases with sulfadiazine, and one each with benzylpenicillin, azithromycin and levofloxacin (**Table 4**).

DISCUSSION

Out of every 100 adults in the Metropolitan Region of Manaus, three to four used some kind of antibiotic over the 15 days preceding the interview. Consumption was higher among women and among people with fair health. Approximately one fifth of the antibiotics consumed were through self-medication, thus highlighting the existence of weaknesses in the regulatory control over these products.

All the data of the present study, including in relation to self-medication, relied on self-reports from the interviewees. The number of people using antibiotics and the true number of medicines recorded may have been higher than what was observed, since the participants could have forgotten to report their use of a medication. In addition, the recording of product names by the research team may not have been adequate in some cases, since medicine packaging or medical prescriptions were not personally verified during the interviews.

Another limiting factor was the fact that the pediatric population, which is an age group that presents high consumption of antibiotics, was not included in this study. According to an analysis on a French database of healthcare service use between 2010 and 2011, about 80% of the children aged 0 to 24 months who presented recurrent coryza consumed some type of antibiotic over a six-month period.[12] Another study conducted in public schools in Chicago in 2004 noted that 40% of the children and adolescents aged 4 to 18 were using antibiotics to treat asthma or recurrent coryza.[13] A household survey on the use of antibiotics among children, teenagers and adults in the United States found

Table 2. Unadjusted and adjusted prevalence ratios (PRs) and 95% confidence interval (CI) of antibiotic use according to study variables. Metropolitan Region of Manaus, 2015 (n = 4,001)

Characteristics	PR (95% CI)	P-value	Adjusted PR (95% CI)	P-value
Sex		<0.001		0.011
Male	1.00		1.00	
Female	1.70 (1.20-2.40)		1.58 (1.11-2.24)	
Age (years)		0.731		
18-24	1.00			
25-34	1.15 (0.72-1.83)			
35-44	1.09 (0.66-1.81)			
45-59	0.85 (0.49-1.47)			
60 and over	0.83 (0.42-1.64)			
Social class		0.181		0.393
A/B	1.00		1.00	
C	1.41 (0.82-2.44)		1.32 (0.77-2.28)	
D/E	1.71 (0.96-3.05)		1.50 (0.84-2.67)	
Education		0.379		
Higher education or above	1.00			
High school	1.55 (0.57-4.18)			
Elementary school	1.04 (0.36-3.06)			
Less than elementary school	1.27 (0.46-3.51)			
Health status		0.020		0.059
Good	1.00		1.00	
Fair	1.63 (1.15-2.32)		1.52 (1.08-2.15)	
Poor	1.42 (0.75-2.72)		1.28 (0.66-2.47)	
Healthcare service use over the last 15 days		0.465		
Did not use	1.00			
Used	1.16 (0.78-1.71)			

Table 3. Person responsible for indication of the antibiotics consumed over the 15 days prior to the interview. Metropolitan Region of Manaus, 2015 (n = 136)

Person responsible for indication	n	%
Physician	110	81.0
Interviewee (upon own account)	18	13.2
Relatives/neighbors	7	5.1
Pharmacist	1	0.7
Total	**136**	**100**

Table 4. Total frequencies of antibiotic consumption and numbers of cases of self-medication with each drug over the last 15 days prior to the interview. Metropolitan Region of Manaus, 2015 (n = 136)

Medicine	ATC code	N	%	N self-medication
Cefalexin	J01DB01	54	39.0	6
Amoxicillin	J01CA04	40	29.4	10
Benzylpenicillin benzathine	J01CE01	6	4.4	1
Ciprofloxacin	J01MA02	5	3.7	-
Sulfadiazine	J01EC02	5	3.7	3
Tetracycline	J01AQA07	5	3.7	4
Azithromycin	J01FA10	4	2.9	1
Levofloxacin	J01MA12	4	2.9	1
Sulfamethoxazole + trimethoprim	J01EE01	3	2.2	-
Ampicillin	J01CA01	2	1.5	-
Norfloxacin	J01MA06	2	1.5	-
Erythromycin	J01FA01	1	0.7	-
Ethambutol	J04AK02	1	0.7	-
Methenamine	J01XX05	1	0.7	
Nitrofurantoin	J01XE01	1	0.7	-
Pyrazinamide	J04AK01	1	0.7	-
Rifampicin	J04AB02	1	0.7	

ATC = anatomical therapeutic chemical classification system.

that out of 71,444 subjects, approximately 5% had had an antibiotic prescribed between 1999 and 2012.[14]

Seasonality affects the consumption of antibiotics: the highest frequency of prescription is usually reported during the fall (autumn) and winter,[15,16] seasons that occur between March and September in most of Brazil. The state of Amazonas presents an equatorial climate, characterized by average temperatures of 26 to 28 °C throughout the year and two seasons: rainy (December to May) and dry (June to November). Particularly in Manaus, there is a predominance of high temperatures during the rainy or "winter" season (December to May), with maximum temperatures of 31 to 33 °C.[17]

Higher consumption of antibiotics among women has also been observed in other studies.[18-20] The habit of taking care of personal health is more common among women, which increases the rate of diagnosis and treatment of diseases in this sex. Furthermore, female anatomical and physiological characteristics favor susceptibility to certain infections, such as urinary tract infections.[21] An international population-based study conducted on approximately 29 million adults in Denmark, Netherlands, Italy, United Kingdom and Germany noted important changes in consumption in these countries over the space of a decade or more, varying internally according to age and sex.[22] In another population-based study conducted between 1998 and 2009 on urban and rural populations in the Netherlands, use of antibiotics was higher in the rural region and among women in both regions.[23]

Consumption of antibiotics has been associated with self-assessment of health as "fair". Individuals with this health status are probably not seriously ill, but their health may be somewhat weakened due to a common cold, fever, pain or common respiratory tract infections. A study conducted in Vellore, southern India, analyzed prescriptions and dispensations in small hospitals, clinics and pharmacies from 2003 to 2005. It found that 41.0% of the drugs were antibiotics, and that their main uses were in cases of upper and lower respiratory tract infections, fever and diarrhea.[24]

In the current study, which was conducted five years after ANVISA introduced regulation of antibiotic sales, approximately one fifth of the antibiotics were used for self-medication. A Brazilian study conducted in 1998 involving 6,000 households in all regions of the country found similar self-medication rates.[25] Analysis on antibiotic sales across Brazil between 2008 and 2012 showed that the change in sales policy regulation in 2010 had little impact in the north of the country, comprising a reduction in sales of around 7%. In the southern and southeastern regions of Brazil, which are more developed regions, these reductions were 13% and 16%, respectively.[26] These reductions were more pronounced in the first year of the new regulation. In the following year, sales in the south and southeast continued to decrease, while in other regions sales increased again and reached almost the same level as before the legislation.[26] An analysis on sales in the state of São Paulo over the same period (2008-2012) also found an immediate reduction in the consumption of oral antibiotics, which was increasing before enactment of the regulation, and found that a stable trend was reached in 2012.[27] The legislation also had little impact on the quality and completion of medical prescriptions, which in over 90% of the cases were incomplete.[28] No population-based studies conducted after implementation of regulation of antibiotic sales are available.

The antibiotics most consumed through self-medication in this analysis, i.e. amoxicillin, cephalexin and tetracycline, can be used to treat infections in the genitourinary tract,[29] respiratory tract[30,31] and skin.[32] Such symptoms are recognized by the lay population, and this is potentially a factor favoring more frequent use of these medicines.

Self-medication is known to be one of the sources of bacterial resistance.[33] Spreading of the disease and occurrences of adverse events are among the problems caused by self-medication, which negatively impacts not only the patient's life, but also the healthcare system.[34]

CONCLUSIONS

Use of antibiotics among adults in the Metropolitan Region of Manaus over the previous 15 days was higher among women and among people with fair health. Around one fifth of the antibiotics were reported to be used through self-medication, i.e. without a medical prescription, contrary to current Brazilian regulations. Enforcement of health regulatory inspections is needed to improve compliance with mandatory prescription of antibiotics and thus contribute towards a culture change that would promote rational use of antibiotics.

REFERENCES

1. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86(2):156-67. doi: 10.4065/mcp.2010.0639.
2. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51-77. doi: 10.1093/cid/ciw118.
3. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322-7. doi: 10.1086/665010.
4. Knight GM, Costelloe C, Murray KA, et al. Addressing the Unknowns of Antimicrobial Resistance: Quantifying and Mapping the Drivers of Burden. Clin Infect Dis. 2018;66(4):612-6. doi: 10.1093/cid/cix765.

5. Resistance RoA. Tackling drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance; 2016. Available from: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Accessed in 2018 (Apr 12).
6. Brasil. Resolução de Diretoria Colegiada (RDC) Nº 20, de 5 de maio de 2011. Dispõe sobre o controle de medicamentos à base de substâncias classificadas como antimicrobianos, de uso sob prescrição, isoladas ou em associação. Brasília: Diário Oficial da União (DOU). Seção 1; 2011. p. 39-41. Available from: http://www.anvisa.gov.br/sngpc/Documentos2012/RDC%2020%202011.pdf?jornal=. Accessed in 2018 (Apr 12).
7. Braoios A, Pereira AC, Bizerra AA, et al. Uso de antimicrobianos pela população da cidade de Jataí (GO), Brasil [The use of antimicrobial drugs by the population in the city of Jataí, State of Goias, Brazil]. Cien Saude Colet. 2013;18(10):3055-60. PMID: 24061032; doi: 10.1590/S1413-81232013001000030.
8. Silva MT, Galvão TF. Use of health services among adults living in Manaus Metropolitan Region, Brazil: population-based survey, 2015. Epidemiol Serv Saúde. 2017;26(4):725-34. PMID: 29069169; doi: 10.5123/S1679-49742017000400005.
9. Programa das Nações Unidas Para o Desenvolvimento. Atlas do Desenvolvimento Humano no Brasil. RM-Manaus. Brasilia: PNUD; 2013. Available from: http://www.atlasbrasil.org.br/2013/pt/perfil_rm/manaus. Accessed in 2018 (Apr 12).
10. Brasil. Associação Brasileira de Empresas de Pesquisa. Critério Brasil 2015 e atualização da distribuição de classes para 2016. São Paulo: ABEP; 2015. Available from: http://www.abep.org/criterio-brasil. Accessed in 2018 (Apr 12).
11. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). ATC/DDD Index. Antiinfectives for systemic use. Oslo: Norwegian Institute of Public Health; 2016 [updated 2016 December 20]. Available from: https://www.whocc.no/atc_ddd_index/?code=J&showdescription=yes. Accessed in 2018 (Apr 12).
12. Belhassen M, De Blic J, Laforest L, et al. Recurrent Wheezing in Infants: A Population-Based Study. Medicine (Baltimore). 2016;95(15):e3404. PMID: 27082618; doi: 10.1097/MD.0000000000003404.
13. Eldeirawi KM, Kunzweiler C, Atek A, Persky VW. Antibiotic use in infancy and the risk of asthma in Mexican American children. J Asthma. 2015;52(7):707-14. PMID: 25584659; doi: 10.3109/02770903.2015.1004338.
14. Frenk SM, Kit BK, Lukacs SL, Hicks LA, Gu Q. Trends in the use of prescription antibiotics: NHANES 1999-2012. J Antimicrob Chemother. 2016;71(1):251-6. PMID: 26462985; doi: 10.1093/jac/dkv319.
15. Safaeian L, Mahdanian AR, Salami S, Pakmehr F, Mansourian M. Seasonality and Physician-related Factors Associated with Antibiotic Prescribing: A Cross-sectional Study in Isfahan, Iran. Int J Prev Med. 2015;6:1. PMID: 25789136; doi: 10.4103/2008-7802.151431.
16. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. Clin Infect Dis. 2012;55(5):687-94. PMID: 22752512; doi: 10.1093/cid/cis509.
17. Instituto Nacional de Metereologia (INMET). Normais climatológicas para o Brasil (1961-1990). Brasília: INMET; 2018. Available from: http://www.inmet.gov.br/portal/index.php?r=clima/normaisClimatologicas. Accessed in 2018 (Apr 12).
18. Blix HS, Engeland A, Litleskare I, Rønning M. Age- and gender-specific antibacterial prescribing in Norway. J Antimicrob Chemother. 2007;59(5):971-6. PMID: 17329270; doi: 10.1093/jac/dkm032.
19. Loikas D, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. BMJ Open. 2013;3(5). pii: e002378. PMID: 23645921; doi: 10.1136/bmjopen-2012-002378.
20. Serna MC, Ribes E, Real J, et al. Alta exposición a antibióticos en la población y sus diferencias por género y edad [High exposure to antibiotics in the population and differences by sex and age]. Aten Primaria. 2011;43(5):236-44. PMID: 21145134; doi: 10.1016/j.aprim.2010.04.015.
21. Hooton TM. Recurrent urinary tract infection in women. Int J Antimicrob Agents. 2001;17(4):259-68. PMID: 11295405.
22. Mor A, Frøslev T, Thomsen RW, et al. Antibiotic use varies substantially among adults: a cross-national study from five European Countries in the ARITMO project. Infection. 2015;43(4):453-72. PMID: 25828936; doi: 10.1007/s15010-015-0768-8.
23. de Jong J, Bos JH, de Vries TW, de Jong-van den Berg LT. Use of antibiotics in rural and urban regions in the Netherlands: an observational drug utilization study. BMC Public Health. 2014;14:677. PMID: 24992967; doi: 10.1186/1471-2458-14-677.
24. Chandy SJ, Thomas K, Mathai E, et al. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, South India. J Antimicrob Chemother. 2013;68(1):229-36. PMID: 22945913; doi: 10.1093/jac/dks355.
25. Marlière GL, Ferraz MB, dos Santos JQ. Antibiotic consumption patterns and drug leftovers in 6000 Brazilian households. Adv Ther. 2000;17(1):32-44. PMID: 10915402.
26. Moura ML, Boszczowski I, Mortari N, et al. The Impact of Restricting Over-the-Counter Sales of Antimicrobial Drugs: Preliminary Analysis of National Data. Medicine (Baltimore). 2015;94(38):e1605. PMID: 26402824; doi: 10.1097/MD.0000000000001605.
27. Kliemann BS, Levin AS, Moura ML, Boszczowski I, Lewis JJ. Socioeconomic Determinants of Antibiotic Consumption in the State of Sao Paulo, Brazil: The Effect of Restricting Over-The-Counter Sales. PLoS One. 2016;11(12):e0167885.
28. Lima SI, Diniz RS, Egito ES, et al. Rationality of Antimicrobial Prescriptions in Community Pharmacy Users. PLoS One. 2015;10(10):e0141615.
29. Charra F, Bourne C, Forissier C, et al. Quality improvement program of adult urinary tract infection management: Review and impact. Med Mal Infect. 2017. 47(8):519-525. PMID: 28869102; doi: 10.1016/j.medmal.2017.07.008.

30. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72. PMID: 17278083.
31. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(2 Suppl):S1-S39. PMID: 25832968; doi: 10.1177/0194599815572097.
32. Niebuhr M, Mai U, Kapp A, Werfel T. Antibiotic treatment of cutaneous infections with Staphylococcus aureus in patients with atopic dermatitis: current antimicrobial resistances and susceptibilities. Exp Dermatol. 2008;17(11):953-7. PMID: 18557929; doi: 10.1111/j.1600-0625.2008.00734.x.
33. Rather IA, Kim BC, Bajpai VK, Park YH. Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi J Biol Sci. 2017;24(4):80812. PMID: 28490950; doi: 10.1016/j.sjbs.2017.01.004.
34. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277-83. PMID: 25859123.

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Are surface and deep learning approaches associated with study patterns and choices among medical students? A cross-sectional study

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ABSTRACT

BACKGROUND: Different approaches to learning can exert considerable influence on the teaching-learning process in medical education. This study aimed to investigate the association of surface and deep learning with study patterns, preferred type of assessment, practices of cheating and quality of sleep among medical students.

DESIGN AND SETTING: Cross-sectional study on medical students enrolled in all six years of a medical school in Juiz de Fora, Brazil.

METHODS: Questionnaires were applied to evaluate learning approaches (R-SPQ-2F), study patterns, sources and choices, and quality of sleep. Students' learning approaches (deep or surface) were assessed in relation to their study patterns, study resources, quality of sleep and whether they cheated in tests.

RESULTS: Among the 710 students included, 43% frequently studied on the night before an exam, 65% had used psychostimulants to study and more than 46% had cheated in an exam. Regarding quality of sleep, most students (53.4%) reported that their quality of sleep was poor, such that 45.3% slept for fewer than five hours before an exam. Those who studied just prior to an exam, used class summaries, preferred multiple-choice questions and cheated during the test had a more surface-learning approach. On the other hand, those who read books, preferred practical exams and slept better had a deeper approach.

CONCLUSION: The type of learning approach was associated with study patterns and choices among medical students. Educators need to be attentive to the type of learning their students use and think of measures that impact teaching and assessment methods.

INTRODUCTION

Students' motivation, educational strategies, types of assessment and different learning approaches are factors that are considered fundamental to medical education. They have an important influence on the teaching-learning process.[1-3] Biggs[4] defined learning approaches as the combination of motivation and strategy that students use in the learning process, which can be "surface" or "deep".

The deep approach comprises the capacity to correlate new and previous knowledge, study comprehensively in order to obtain the "entire picture" and search for meaning and implications for the acquired knowledge.[5] Its strategy is based on personal commitment to the learning process and its motivation is intrinsic, in the search for self-fulfillment.[4] This contrasts with the surface approach, which is the tendency to choose the quickest way to accomplish the task, in which students study the material in a linear manner, do not ask in-depth questions, do not show proper interest in the subject and rely on memory instead of comprehension.[5] Students with surface approaches tend to achieve the minimum necessary to avoid failure at school.[6]

Previous studies have pointed out that the same students can have varying approaches, depending on the subject that they are studying, levels of apprehension and work overload.[7,8] Understanding these learning approaches could have important repercussions on students' academic life. Mattick et al.[9] showed that students with a deep approach tend to be more organized, monitor their studies better and exert a greater effort to learn, such that their performance in tests is better. The same results were found by McManus et al.,[10] who found that students with a deep approach had better outcomes in final exams.

Another important factor that is seldom studied within medical education, and which seems to have an important influence on students' learning and even on students' health, is study patterns. It has been shown that medical students usually have a very exhausting routine with long self-study hours,[11] poor sleep quality,[12] high caffeine consumption[13] and failure to efficiently manage their study time.[14] This dysfunctional study routine seems to be closely associated with learning approaches. However, despite frequent anecdotal descriptions within the educational context, few studies (and, to our knowledge, none in Brazil) have evaluated this relationship. Understanding this relationship could help educators to identify learning approaches in order to provide interventions and make curricular changes that might help students' academic performance and health outcomes.

OBJECTIVE

Thus, the objective of this study was to investigate the associations of surface and deep learning approaches with study patterns, preferred type of assessment method, practices of cheating and quality of sleep among medical students. Our hypothesis was that students whose approach was more towards surface learning would tend to use study methods that required less work (e.g. summaries or cheating), would have poorer quality of sleep (due to studying more frequently on the night before exams) and would choose assessment methods that were more superficial (multiple-choice tests rather than simulations or clinical assessments).

METHOD

Study design, ethics and participants

This cross-sectional study was conducted in 2016 and included students from all six years of medical school at the Federal University of Juiz de Fora (Universidade Federal de Juiz de Fora, UFJF), in Juiz de Fora (MG), Brazil. Students who were not in Brazil due to exchange programs, who were doing their clerkship in another city, who were not present when data was collected, or who did not wish to participate were excluded.

The project was approved by the Research Ethics Committee of the University Teaching Hospital of UFJF, under report no. 1.147.798/2015. All participating students signed a consent form.

Instruments

The self-report questionnaire that was used took approximately 20 minutes to fill out and collected the following data:

- Sociodemographic data: age, ethnicity, gender, marital status and course level in which students were enrolled.
- Study patterns and study resources: for this study, six questions were developed, dealing with:
  1. the number of hours dedicated to studies each week;
  2. means used for routine study (books and study guides, class notes, professors' slides and internet research);
  3. methods used to study for tests (schemes, summaries, books, audios and videos);
  4. how often the students waited until just before the test to do their studying (five options, ranging from "never" to "always");
  5. whether students cheated ("yes" or "no"); and
  6. how often students used stimulants while studying (five options, ranging from "never" to "always") and the type of stimulant used (students were asked to declare which stimulant(s) they used).
- Quality of sleep and its relationship with students' routines: four questions relating to students' quality of sleep and its relationship with their studying were used:
  1. quality of sleep (four options, ranging from "very poor" to "very good");
  2. how often students had problems staying awake while driving or at social events (four options, ranging from "never" to "three or more times a week");
  3. how often students had problems sleeping due to worrying about tests (four options, ranging from "never" to "three or more times a week"); and
  4. how many hours of sleep students had on the night before a test (three options: "fewer than five hours", "five to eight hours" or "more than eight hours").
- Revised two-factor version of the Study Process Questionnaire (R-SPQ-2F): developed by Biggs et al.[2] and validated for use in Brazil by Costa.[15] This questionnaire is made up of two 10-item scales (deep approach and surface approach) in a Likert format ("never" to "always or almost always"). Each scale has two subscales that each consists of five questions referring to motivation and five questions referring to strategy. Thus, four categories are formed: deep motivation (e.g. "I find that at times studying gives me a feeling of deep personal satisfaction"); deep strategy (e.g. "I find most new topics interesting and often spend extra time trying to obtain more information about them."); surface motivation (e.g. "My aim is to pass the course while doing as little work as possible"); and surface strategy (e.g. "I find that the best way to pass examinations is to try to remember answers to likely questions"). The responses are coded as 1 = "never" to 5 = "always or almost always" and the results range from 10 to 50 points for each scale. The "deep approach" scale score is based on the sum of the deep strategy subscale (five questions) and the deep motivation subscale (five questions), and higher scores denote use of a deeper approach. The score for the "surface approach" scale is based on the sum of the surface strategy subscale (five questions) and the surface motivation subscale (five questions), and higher scores denote use of a more surface approach).

Statistical analysis

A descriptive analysis was carried out on each variable, using frequency and percentage, or mean and standard deviation. An inferential analysis was then conducted. We firstly compared the means of students' learning approaches (deep or surface), according to their study patterns, study resources, quality of sleep and whether they cheated in tests. For this, t tests for independent samples were used. We then correlated students' learning approaches with their preferred assessment using the Spearman correlation test. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21 (SPSS Inc.). $P < 0.05$ was considered significant.

RESULTS

Out of the total of 1,007 students officially registered in this medical school, 710 students were included (response rate 70.5%): 265 (37.3%) in the preclinical phase (1st and 2nd years), 233 (32.8%) in the clinical phase (3rd and 4th years) and 212 (29.9%) in the clerkship phase (5th and 6th years). The majority of the students were female (55.4%), single (98.0%) and white (66.9%), and their mean age was 22.11 years (standard deviation, SD: 3.11).

Table 1 shows the students' study patterns, study resources, quality of sleep and cheating in tests. Most students (61.7%) were studying for six or more hours per week outside of class activities and the aides that they used were most frequently books (68.5%), followed by class notes (25.6%) and teachers' slides (23.4%). Almost 43% frequently or always studied on the night before an exam and they used class summaries that they themselves or colleagues wrote (67.7%), books (35.8%) and study schemes (11.1%) to prepare for exams. A total of 46% of the students had cheated in an exam and 65% had used psychostimulants to study (40% frequently or always). Among the students who reported using stimulants, 73.5% of them used coffee, 17.0% caffeine pills, 16.6% energy drinks, 7.2% guarana seed powder, 3.6% methylphenidate and 4% other stimulants. Regarding the students' quality of sleep, most (53.4%) reported that it was poor or very poor and 45.3% reported that they had fewer than five hours of sleep before an exam.

Table 2 shows a comparison of the students' learning approaches (deep or surface) according to their study patterns, study resources, quality of sleep and if they cheated on tests. We found that those who had a more superficial learning approach were those who studied on the night before an exam used professors' slides, class audios and class summaries, and those who cheated in tests. On the other hand, those using or reading books and sleeping better learned more deeply.

Table 3 shows the correlation between learning approaches and preferred types of assessments. Those with deeper learning

Table 1. Students' study patterns, study resources, quality of sleep and cheating in tests

	n	%
Hours of study per week		
1 to 2	29	4.1
3 to 4	78	11.0
4 to 5	81	11.4
5 to 6	84	11.8
More than 6	438	61.7
Routine means of study		
Books and study guides	486	68.5
Classroom notes	182	25.6
Professors' slides	166	23.4
Internet	154	21.7
Use of stimulants		
No	249	35.1
Yes, once	21	3.0
Yes, rarely	157	22.1
Yes, frequently	206	29.1
Yes, always	76	10.7
Waiting until just before exam to study		
Never	27	3.8
Rarely	88	12.4
Sometimes	282	39.8
Frequently	270	38.1
Always	41	5.8
Methods used to study for tests		
Schemes	79	11.1
Summaries	481	67.7
Books	254	35.8
Audios	60	8.5
Videos	62	8.7
Cheating		
Yes	326	46.6
No	373	53.4
Quality of sleep		
Very poor	84	11.9
Poor	293	41.5
Good	271	38.4
Very good	58	8.2
How often students had problems staying awake while driving or at a social event		
Never	176	25.0
Less than once a week	191	27.1
1 to 2 times a week	211	29.9
3 or more times a week	127	18.0
How often students had problems sleeping because they were worried about a test		
Never	382	54.3
Less than once a week	127	18.0
1 to 2 times a week	121	17.2
3 or more times a week	74	10.5
How many hours students were sleeping on the night before an exam	318	45.3
Fewer than 5 hours	356	50.7
Between 5 and 8 hours	28	4.0

Table 2. Students' learning approaches (deep or surface) according to their study patterns, study resources, quality of sleep and cheating in tests

	Biggs Deep R-SPQ-2F Mean (SD)	P	Biggs Surface R-SPQ-2F Mean (SD)	P
Study resources				
Books				
Yes	29.98 (6.60)	**0.009**	21.50 (5.87)	**< 0.001**
No	28.58 (6.37)		24.23 (6.77)	
Class notes				
Yes	29.33 (6.23)	0.634	22.36 (6.63)	0.999
No	29.61 (6.67)		22.36 (6.18)	
Professors' slides				
Yes	27.73 (6.45)	**< 0.001**	24.25 (6.77)	**< 0.001**
No	30.09 (6.50)		21.79 (6.03)	
Internet				
Yes	28.91 (6.59)	0.183	22.22 (6.70)	0.755
No	29.71 (6.54)		22.40 (6.18)	
Methods used to study for tests				
Self-study schemes				
Yes	30.02 (7.05)	0.493	22.35 (7.48)	0.981
No	29.48 (6.50)		22.36 (6.14)	
Summaries				
Yes	28.89 (6.45)	**< 0.001**	22.86 (6.40)	**0.002**
No	30.90 (6.58)		21.31 (5.94)	
Books				
Yes	30.82 (6.40)	**< 0.001**	20.62 (5.61)	**< 0.001**
No	28.81 (6.54)		23.34 (6.45)	
Audios				
Yes	29.24 (6.55)	0.716	24.18 (6.51)	**0.020**
No	29.56 (6.56)		22.19 (6.25)	
Videos				
Yes	30.29 (7.36)	0.347	21.09 (6.08)	0.100
No	29.46 (6.47)		22.48 (6.30)	
Study characteristics				
Hours studied per week				
1-5 hours	27.50 (6.28)	**< 0.001**	23.58 (6.64)	**< 0.001**
6 or more	30.79 (6.41)		21.60 (5.95)	
Waiting until night before to study				
Frequently/always	26.68 (6.15)	**< 0.001**	24.61 (6.44)	**< 0.001**
Never/rarely/sometimes	31.73 (5.96)		20.58 (5.59)	
Use of stimulants				
Frequently/always	29.58 (6.99)	0.865	22.73 (6.46)	0.208
Never/rarely/sometimes	29.49 (6.26)		22.12 (6.18))	
Sleep				
Hours slept on night before an exam				
Up to 5 hours	29.15 (6.81)	0.156	22.92 (6.73)	**0.049**
5 or more	29.86 (6.37)		21.96 (5.90)	
Quality of sleep				
Very good/good	29.95 (6.43)	0.128	21.90 (6.05)	0.064
Poor/very poor	29.19 (6.67)		22.79 (6.48)	
Difficulty staying awake while driving or at social events				
Once or more per week	28.96 (6.61)	**0.025**	22.82 (6.36)	0.071
Less than once	30.08 (6.50)		21.96 (6.22)	
How often does the student have problems sleeping due to worrying about tests?				
Once or more per week	29.35 (6.88)	0.618	23.09 (6.59)	0.061
Less than once	29.63 (6.45)		22.10 (6.15)	
Cheating				
Do you cheat?				
Yes	28.19 (6.25)	**< 0.001**	23.45 (6.33)	**< 0.001**
No	31.14 (6.58)		20.97 (5.95)	

approaches preferred practical exams (standardized or real-patient assessments) and those with more surface approaches preferred multiple-choice questions (**Table 3**).

DISCUSSION

Medical students' exhausting routine, as found during this study, has been described extensively in the scientific literature. It includes long hours of study, little sleep, much content absorbed passively, surface learning and a tendency towards greater study loads on days preceding tests.[13,14,16]

Nevertheless, our findings attempt not only to describe the study routine, but also to try to understand how surface or deeper learning might influence students. It was found that students with a surface approach had poorer quality of sleep and more frequently chose to study just before the exam; they used materials and summaries originating from classes, cheated more frequently and exhibited greater preference for multiple-choice questions. On the other hand, students with a deep approach chose to read books and preferred practical exams with patients, whether real or simulated. From this data, we observed that the type of approach is highly linked to the students' study routine and health.

In relation to the quality of sleep, a study on university students in all disciplines showed that their quality of sleep was poorer during testing periods, with fewer hours of sleep and increased reporting of symptoms compatible with insomnia.[13] Another study, specifically on medical students, showed that students with poorer study outcomes tended to present more sleep-related problems during testing periods.[17] Those findings were also observed in our study. Students with a surface approach presented poorer quality and fewer hours of sleep before tests than did students with a deep approach. They also used more psychostimulants. This can be explained by their limited strategy of basic memorization of the subject matter close to the test day, without integrating prior knowledge and with probably a worse academic performance that students who used a deep approach. This is related to and corroborated by data found in the literature.[17]

Table 3. Correlation between Biggs study approach (surface or deep) and methods of evaluation preferred by students

	Biggs Deep	Biggs Surface
SP	0.114**	-0.032
Real patient	0.136**	-0.079*
Student SP	-0.012	0.029
MCQ	-0.169	0.093*
Open	-0.039	0.008
Open and MCQ	-0.018	-0.060
Individual work	-0.018	0.013
Group work	-0.020	0.001

**P < 0.01; *P < 0.05.

SP = simulated patient; MCQ = multiple-choice questions.

Another point to be highlighted is the practice of cheating. The prevalence of cheating found in our study (46%) was lower than what was reported in a study in India (74%)[18] but was higher than in Saudi Arabia (29%),[19] Ethiopia (19.8%)[20] and the United States (2%).[21] We found that cheating was greater among students with a more surface learning approach. Those students would have a superficial motive for studying, which was simply pass the subject. Cheating is one way to more easily obtain a passing grade.[2] Our findings were also in accordance with those of another study in which it was found that students who used books as study resources (deep approach) had a lower rate of dishonesty in academic settings, which included cheating less.[22] Regarding preferred assessment methods, students with deep learning tended to prefer practical methods of assessment based more on ability and attitude, by means of using real or simulated patients, while those with a more superficial profile tended to prefer multiple-choice tests, which are related to more cognitive and more immediate knowledge.[23]

The above results provide further support for Bigg's learning approaches theory,[4] in which students with deep approaches tend to study comprehensively in order to obtain the entire picture as observed in their study resources (books instead of summaries), while students with surface approaches tend to avoid failure at school by doing the minimum needed (cheating, for example) and rely on memory instead of comprehension (choosing multiple-choice assessments and studying late on the night before an exam, as shown by their poor quality of sleep).

These associations could serve to underwrite future interventions regarding changes to the type of learning (from surface to deep) that could influence students' study routines positively, since such changes would lead to students being less stressed and spending less time memorizing cognitive content in the days preceding assessments. In fact, the use or nonuse of surface or deep strategies is closely related to how certain information is passed on to students. It is influenced by diverse factors, such as professors' attitudes and enthusiasm, the type of subject studied, methods used for studying and students' enthusiasm.[1,3] Therefore, some curricular changes could be envisaged, such as changing to a student-centered method instead of a teacher-centered method, providing more interaction between students, enhancing contact with patients in the early years of medical training, using active educational strategies (team-based learning, problem-based learning, flipped classroom, games and case-based learning, among others) and developing different types of assessments (portfolio, objective structured clinical examination and Mini-Clinical Evaluation Exercise for Trainees, among others). These could potentially shift students' learning approaches and also enhance the learning process, which might indirectly impact health outcomes and performance.

McManus et al.[10] showed that approaches towards knowledge acquisition are dynamic processes. They are influenced not

only by ways of studying but also by the means used to evaluate the content. In this context, the study resources used by students may say more about their strategies for assimilating content than might their results from assessments. Wilson and Fowler[1] compared two groups of students who took a course of the same content and duration, but in which one used a conventional learning and assessment model and the other used an active model. The group that took the course with the active learning model was found to have a higher level of strategies and deeper motives in approaching content.

Educators need to be attentive to the type of learning strategy that their students use, given that the surface approach may be associated with negative consequences for the students who use this approach. Learning approaches can be modified through methods that are centered more on students and on interaction, and through using fewer cognitive assessments.

The present study had some limitations that need to be borne in mind. Although the questionnaire was applied to students in different year groups during the same period of the academic year, the test schedules for each semester are different. Moreover, the stress levels relating to individual students' extracurricular activities were not evaluated. These factors may have influenced students when filling out the questionnaires. Another detail to be taken into consideration is that individuals with prior sleep disturbances or susceptibility to addiction to psychostimulants may present distinct results within the study population. Considering that learning methods, along with the other variables analyzed, are dynamic processes, there is a need for a longitudinal study. It is also worthwhile pointing out that our results refer only to one Brazilian medical school and, therefore, need to be corroborated in other institutions. Furthermore, this was a quantitative study with application of questionnaires. Use of qualitative methods and semi-structured interviews could help in further understanding our results in future studies. Finally, some factors investigated in the present study (e.g. study patterns/resources and cheating) do not have specific and gold standard instruments in the literature. Therefore, we decided to use questions that we created or adapted from previous studies. This was in line with previous studies published in high-impact journals that have used self-created adapted instruments to assess cheating[19,20,21] and study patterns/resources.[16,24,]

CONCLUSIONS

The type of learning approach used (surface or deep) is associated with study patterns, preference for type of assessments, practices of cheating and the quality of sleep among medical students. Educators need to be attentive to the type of learning that their students use and need to think about measures that will have a positive impact on the interactivity between teaching methods and assessments, and on students' quality of learning.

REFERENCES

1. Wilson K, Fowler J. Assessing the impact of learning environments on students' approaches to learning: Comparing conventional and action learning designs. Assessment & Evaluation in Higher Education. 2005;30(1):87-101. doi: 10.1080/0260293042003251770.
2. Biggs J, Kember D, Leung DY. The revised two-factor Study Process Questionnaire: R-SPQ-2F. Br J Educ Psychol. 2001;71(Pt 1):133-49. PMID: 11307705.
3. Ferris HA, O'Flynn D. Assessment in Medical Education; What Are We Trying to Achieve? International Journal of Higher Education. 2015;4(2):139-144. doi: 10.5430/ijhe.v4n2p139.
4. Biggs J. What do inventories of students' learning processes really measure? A theoretical review and clarification. Br J Educ Psychol. 1993;63(Pt 1):3-19. PMID: 8466833.
5. Aharony N. The use of deep and surface learning strategies among students learning English as a foreign language in an Internet environment. Br J Educ Psychol. 2006;76(4):851-66. PMID: 17094889; doi: 10.1348/000709905X79158.
6. Teoh HC, Abdullah MC, Roslan S, Mohad Daud S. Assessing students approaches to learning using a matrix framework in a Malaysian public university. Springerplus. 2014;3:54. PMID: 24600539; doi: 10.1186/2193-1801-3-54.
7. Dart BC, Clarke JA. Helping students become better learners: a case study in teacher education. Higher Education. 1991;22(3):317-35. doi: 10.1007/BF00132294.
8. Groves M. Problem-based learning and learning approach: is there a relationship? Adv Health Sci Educ Theory Pract. 2005;10(4):315-26. PMID: 16362620; doi: 10.1007/s10459-005-8556-3.
9. Mattick K, Dennis I, Bligh J. Approaches to learning and studying in medical students: validation of a revised inventory and its relation to student characteristics and performance. Med Educ. 2004;38(5):535-43. PMID: 15107087; doi: 10.1111/j.1365-2929.2004.01836.x.
10. McManus IC, Richards P, Winder BC, Sproston KA. Clinical experience, performance in final examinations, and learning style in medical students: prospective study. BMJ. 1998;316(7128):345-50. PMID: 9487168.
11. Barbosa J, Silva A, Ferreira MA, Severo M. The impact of students and curriculum on self-study during clinical training in medical school: a multilevel approach. BMC Med Educ. 2017;17(1):9. PMID: 28086868; doi:10.1186/s12909-016-0846-3.
12. Corrêa CC, Oliveira FK, Pizzamiglio DS, Ortolan EVP, Weber SAT. Sleep quality in medical students: a comparison across the various phases of the medical course. J Bras Pneumol. 2017;43(4):285-9. PMID: 29365004; doi:10.1590/S1806-37562016000000178.
13. Zunhammer M, Eichhammer P, Busch V. Sleep quality during exam stress: the role of alcohol, caffeine and nicotine. PloS One. 2014;9(10):e109490. PMID: 25279939; doi: 10.1371/journal.pone.0109490.
14. Bickerdike A, O'Deasmhunaigh C, O'Flynn S, O'Tuathaigh C. Learning strategies, study habits and social networking activity of undergraduate medical students. Int J Med Educ. 2016;7:230-6. PMID: 27424041; doi: 10.5116/ijme.576f.d074.

15. Costa SG. Validação para o Brasil da escala Revised two-factor Study Process Questionnaire (R-SPQ-2F) [thesis]. São Paulo: Enfermagem, Universidade de São Paulo; 2010. doi: 10.11606/T.83.2010.tde-26042010-143400.
16. Taylor JA, Shaw CM, Tan SA, Falcone JL. Are the kids alright? Review books and the internet as the most common study resources for the general surgery clerkship. Am J Surg. 2018;215(1):191-5. PMID: 28237045; doi: 10.1016/j.amjsurg.2017.01.036.
17. Ahrberg K, Dresler M, Niedermaier S, Steiger A, Genzel L. The interaction between sleep quality and academic performance. J Psychiatr Res. 2012;46(12):1618-22. PMID: 23040161; doi: 10.1016/j.jpsychires.2012.09.008.
18. Babu TA, Joseph NM, Sharmila V. Academic dishonesty among undergraduates from private medical schools in India. Are we on the right track? Med Teach. 2011;33(9):759-61. PMID: 21592022; doi: 10.3109/0142159X.2011.576717.
19. Abdulghani HM, Haque S, Almusalam YA, et al. Self-reported cheating among medical students: An alarming finding in a cross-sectional study from Saudi Arabia. PloS One. 2018;13(3):e0194963. PMID: 29596538; doi: 10.1371/journal.pone.0194963.
20. Desalegn AA, Berhan A. Cheating on examinations and its predictors among undergraduate students at Hawassa University College of Medicine and Health Science, Hawassa, Ethiopia. BMC Med Educ. 2014;14:89. PMID: 24885973; doi: 10.1186/1472-6920-14-89.
21. Dyrbye LN, Massie FS Jr, Eacker A, et al. Relationship between burnout and professional conduct and attitudes among US medical students. JAMA. 2010;304(11):1173-80. PMID: 20841530; doi: 10.1001/jama.2010.1318.
22. Oran NT, Can HÖ, Senol S, Hadimli AP. Academic dishonesty among health science school students. Nurs Ethics. 2016;23(8):919-31. PMID: 26002938; doi: 10.1177/0969733015583929.
23. Wilkinson TJ, Frampton CM. Comprehensive undergraduate medical assessments improve prediction of clinical performance. Med Educ. 2004;38(10):1111-6. PMID: 15461657; doi: 10.1111/j.1365-2929.2004.01962.x.
24. Boni R, Paiva CE, de Oliveira MA, et al. Burnout among medical students during the first years of undergraduate school: Prevalence and associated factors. PloS One. 2018;13(3):e0191746. PMID: 29513668; doi: 10.1371/journal.pone.0191746.

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Comparison of the effects of albumin and crystalloid on mortality among patients with septic shock: systematic review with meta-analysis and trial sequential analysis

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KEY WORDS:
Albumins.
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ABSTRACT

BACKGROUND: This study aimed to compare the effects on mortality of albumin and crystalloid, used for fluid resuscitation among adult patients with septic shock, through conducting a meta-analysis and trial sequential analysis (TSA).

DESIGN AND SETTING: Meta-analysis and TSA conducted at Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.

METHODS: Data were collected from several major databases including MEDLINE, EMBASE, Clinical Trials.gov and Cochrane Central Register of Controlled Trials. Studies that compared the effects of albumin therapy versus crystalloid therapy on mortality among adult septic shock patients were eligible for inclusion in the analyses. The study name, year of publication, country of the trial, albumin concentration, type of crystalloid and all reported mortalities at different follow-up endpoints were extracted.

RESULTS: Compared with crystalloid, albumin did not decrease all-cause mortality at the final follow-up. However, in TSA, the required information size was not achieved in all groups, which means that the effect size was not definitive and further RCTs are needed to confirm or deny these findings

CONCLUSIONS: Compared with crystalloid solutions, albumin was unable to decrease all-cause mortality. However, TSA indicated that these results could be false-negative. Additional randomized controlled trials are needed to clarify this discrepancy.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a disordered response of the body to infection.[1] Septic shock is a phenomenon relating to sepsis and is a serious disorder involving both the circulatory system and cell metabolism. During septic shock, extremely low blood pressure is observed, and this requires use of a vasoactive drug after adequate volumetric resuscitation has been applied, in order to maintain average blood pressure ≥ 65 mmHg and lactate concentration ≥ 2 mmol/l. Septic shock is the most life-threatening subtype of sepsis, with a mortality rate of 20% to 45%.[2] Fluid resuscitation is a key component of treatments for sepsis and septic shock.

Over the past 30 years, many randomized clinical trials (RCTs) and systematic reviews[3-8] that evaluated the therapeutic effects of various fluid resuscitation therapies on sepsis concluded that crystalloid and albumin were the most beneficial therapeutic agents, while use of artificial colloid was associated with a higher death rate and with adverse events. However, few RCTs and systematic reviews have compared the therapeutic effects of crystalloid and albumin regarding septic shock.[9-13] Moreover, the researchers involved in the studies available differed in their conclusions.[14-21]

According to the findings from the Enhanced Recovery after Surgery (ERAS) study,[14] albumin does not reduce the mortality rate due to septic shock, whereas the findings from another large RCT called ALBIOS (NCT00707122)[15] concluded that fluid resuscitation using albumin could reduce the mortality rate from septic shock. In 2014, contrary results were reported in a meta-analysis by Patel et al.,[16] which found that there was no difference between the effects from albumin and crystalloid treatment, while another meta-analysis by Xu et al.[17] reported that albumin treatment had positive results with regard to reducing the mortality rate among adult patients with septic shock.

These studies have shown that it is not yet a foregone conclusion that albumin is superior to crystalloid for reducing the mortality rate in septic shock cases. In 2015, the Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP) RCT (NCT01337934)[18] specifically compared 4%

albumin and lactated Ringer's solution with crystalloid, regarding the mortality rate among patients with septic shock. They found that resuscitation with 4% albumin, as compared with lactated Ringer, did not improve the survival rate among patients with septic shock at 30 days.

The previous descriptions show that, to date, no research findings regarding the preferred method for fluid resuscitation in septic shock cases have yet been conclusive. Our team proposed to conduct a meta-analysis focusing on the differences in the effects of albumin and crystalloid on the mortality rate due to septic shock. Moreover, we used the trial sequential analysis (TSA, available at www.ctu.tsa) method to further analyze the results from the meta-analysis. TSA is a newly proposed statistical analysis method that can improve the strength and accuracy of meta-analyses through applying an overall quantity analysis to it.

METHODS

Search strategy

This study was not registered. It was conducted in accordance with the guidance from the Cochrane Collaboration. The study findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[22,23]

Data were collected from the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). The following keywords were used as searching terms: albumin, crystalloid, sepsis, pyemia*, pyohemia*, blood poisoning, mortality and survival, or prognos* and predict*. No language restrictions were placed on the search results. An additional search was carried out in Clinical Trials.gov. The date range of our search was defined as until February 27, 2017 (**Table 1**).

Eligibility criteria

The following types of studies were eligible for inclusion:

1. RCTs in which fluid resuscitation comparing albumin and crystalloid solution in adult patients with septic shock was studied; and
2. studies in which the mortality rate among patients with septic shock was assessed.

Data extraction

Two reviewers (YZ and JBX) independently reviewed full-text manuscripts from the trials thus included. Any disagreement between the two reviewers was resolved through discussion or through consultation with a third reviewer (KM). Data extraction included the following: study name, year of publication, country in which the trial was conducted, trial centers, albumin concentration in the trial, type of crystalloid and all-cause mortality reported at different follow-up endpoints (CHX and XJD). The investigators also tried to contact the authors of the studies included to consult with them and clarify their data and concrete methods, when necessary (done by XJD).

Risk of bias of studies included

The risk of bias of each study was independently assessed through using the Cochrane Risk of Bias (RoB) table,[23] in the Review Manager (RevMan) software (version 5.3.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen) The RoB table considers six domains:

1. selection bias (relating to sequence generation and allocation concealment);
2. performance bias (blinding of participants and personnel);
3. measurement bias (blinding of outcome assessment);
4. loss-to-follow-up bias (any incompleteness of outcome data);
5. publication bias (freedom from selective reporting); and
6. other bias.

The overall risk of bias of individual studies was classified into the following categories: low risk of bias, unclear risk of bias and high risk of bias. Low risk was defined as a low risk of bias in all domains; an unclear risk was defined as an unclear risk of bias in at least one domain with no domains showing a high risk of bias; and high risk was defined as a high risk of bias in one or more domains. The risk of bias of the studies included is shown in **Table 2**.

Grading the quality of evidence

The quality of evidence was assessed by means of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.[24] The quality of evidence was classified as high, moderate, low or very low, based on judgment of the

Table 1. Search strategies used in MEDLINE, Embase and Cochrane databases

Databases	Search strategy
MEDLINE(via PubMed)	((((“Sepsis”[Mesh]) OR (((((((sepsis[Title/Abstract]) OR septic [Title/Abstract]) OR Pyemia*[Title/Abstract]) OR Pyohemia* [Title/Abstract]) OR Pyaemia*[Title/Abstract]) OR Septicemia* [Title/Abstract]) OR Blood Poisoning[Title/Abstract]))) AND ((“Albumins”[Mesh]) OR albumin*[Title/Abstract])) AND (((“Mortality”[Mesh]) OR “Survival”[Mesh]) OR ((((((mortality [Title/Abstract]) OR fatality[Title/Abstract]) OR survival[Title/Abstract]) OR death[Title/Abstract]) OR prognos*[Title/Abstract]) OR predict*[Title/Abstract]))
EMBASE	(‘sepsis’/exp OR ((Sepsis OR septic OR Pyemia* OR Pyohemia* OR Pyaemia* OR Septicemia*OR ‘Blood Poisoning’):ab,ti)) AND (‘albumin’/exp OR albumin*:ab,ti) AND (((mortality OR fatality OR death OR prognos* OR predict* OR survival) :ab,ti) or ‘mortality’/exp)
Cochrane Central Register of Controlled Trials	([Sepsis] or (sepsis:ti,ab,kw or sepic:ti,ab,kw or Pyemia*:ti,ab,kw or Pyohemia*:ti,ab,kw or Pyaemia*:ti,ab,kw) or (Septicemia*:ti,ab,kw or Blood Poisoning:ti,ab,kw)) and ([Albumins] or albumin*: ti,ab, kw) and ([Mortality] or [Survival] or mortality:ti,ab,kw or survival:ti,ab,kw or fatality:ti,ab,kw or death:ti,ab,kw or prognos* :ti,ab,kw or predict*:ti,ab,kw)

outcome of all-cause mortality, with regard to the risk of bias, inconsistency, indirectness, imprecision and other considerations.[24] GRADE was applied firstly to each comparison of fluid resuscitation using human albumin and secondly to each predefined risk-of-bias subgroup. The summary shown in **Table 3** was constructed using GRADE pro (version 3.6).

Statistical analysis

The outcomes from the trials included were pooled in terms of either relative risk (RR [risk ratio = relative risk]) for dichotomous outcomes or mean differences for continuous outcomes with 95% confidence intervals (CIs). All statistical analyses were performed using the RevMan 5.3.3 software and the Trial Sequential Analysis software (version 0.9 beta). A random-effects model (Mantel-Haenszel method) was used in the presence of statistical heterogeneity or if the situation was judged to present potential for clinical heterogeneity.[25]

Findings in which the 95% CI boundaries of TSA did not include null (< 1.00 or > 1.00) were considered statistically significant. The risk of type I error was maintained at 5% with a power of 80%. The anticipated relative risk and the event proportion in the control arm refer to the results from our meta-analysis. Publication bias was evaluated using a funnel plot (**Figure 1**). Rational sensitivity analysis was not conducted.

RESULTS

Study identification and selection

A total of 3,981 records were identified in the initial search, and of these, 466 records were removed as duplicates. The remaining 3,515 records were screened. After an assessment of the titles and abstracts, 3,465 articles were excluded as not relevant to the analyses. A total of 50 studies were identified as potentially eligible for inclusion. After screening the full-text articles, 12 studies that compared albumin with crystalloid solutions among patients with septic shock were found to be eligible for inclusion. Of these, six studies did not meet the first eligibility criterion (i.e. prospective RCTs) and were excluded (**Supplementary file**). Thus, in the end, only six studies[14,15,18-21] representing 3,088 patients with septic shock were included in the meta-analysis and TSA (**Figure 2**, flow chart). The characteristics of the studies included are listed in **Table 4**.

Characteristics of studies included

The characteristics of the studies included are shown in **Table 4**. All-cause mortality at 28 days was explored in four studies.[14,18,20,21] Ninety-day mortality rates were shown in two trials.[15,21] Hospital discharge rates were reported in one study.[19] Volume expansion for fluid resuscitation was done using 20% albumin in two trials;[14,15] 4% or 5% albumin in three studies;[18-20] and both concentrations in one trial.[16] Normal saline was used as the crystalloid solution in four trials,[14,19-21] and lactated Ringer's solution was used in one trial.[18] The remaining trial[10] included different kinds of crystalloid products. Four trials had a low or unclear risk of bias[14,15,18,20] and two studies had a high risk of bias.[14,16]

All-cause mortality at different follow-ups after use of albumin, compared with crystalloid

Meta-analysis

Compared with crystalloid solutions, human albumin showed no benefit regarding all-cause mortality at the final follow-up (RR: 0.91; 95% CI: 0.83-1.00; P = 0.05; I^2 = 0%; **Figure 3**). Similarly, use of albumin was not found to have decreased 28-day mortality[14,18,20,21] (RR 0.96; 95% CI: 0.83-1.11; I^2 = 1%) or 90-day[18,21] mortality (RR: 0.89; 95% CI: 0.79-1.00; P = 0.06; I^2 = 0%) (**Figure 4**).

TSA

A diversity-adjusted information size of 4,815 patients was calculated using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%), D2 = 0%, an anticipated RR of 10.0% (**Table 3**) and an event proportion of 39% in the control arm (**Table 3**). The cumulative z curve was constructed using a random-effects model. TSA showed that, out of the required sample size of 4,815 patients, a sample size of 3,088 patients was accrued. The cumulative z curve touched the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit (**Figure 5**). This outcome indicates that the result was possibly a false negative because the required sample size was not met.

Table 2. Quality evaluation on the studies included

Study name	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Rackow et al.[19]	unclear	unclear	high risk	low risk	low risk	low risk	unclear	high risk
SAFE study[20]	low risk	low risk	low risk	low risk	low risk	low risk	unclear	unclear
EARSS study[14]	low risk	low risk	unclear	low risk	low risk	low risk	low risk	unclear
RASP study[18]	low risk	low risk	low risk	low risk	low risk	low risk	unclear	unclear
CRYSTAL study[21]	low risk	low risk	high risk	low risk	low risk	unclear	low risk	high risk
ALBIOS study[15]	low risk	low risk	unclear	low risk	low risk	low risk	low risk	unclear

Table 3. Quality-of-evidence summary table according to GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-cause mortality at final follow-up after use of albumin	Crystalloid	Relative risk (95% CI)	Absolute		
All-cause mortality at final follow-up after use of albumin, compared with crystalloids												
6	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	466/1282 (36.3%)	705/1806 (39%) 44.6%	RR 0.91 (0.83 to 1)	35 fewer per 1,000 (from 66 fewer to 0 more) 40 fewer per 1,000 (from 76 fewer to 0 more)	Moderate	Critical
All-cause mortality at final follow-up after use of different albumin concentrations, compared with crystalloid - hyperoncotic (20% albumin)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	339/957 (35.4%)	384/956 (40.2%) 38.1% 35.4%	RR 0.88 (0.79 to 0.99)	48 fewer per 1,000 (from 4 fewer to 84 fewer) 46 fewer per 1,000 (from 4 fewer to 80 fewer) 18 more per 1,000 (from 92 fewer to 177 more)	High	Critical
Effect of use of albumin versus crystalloid on all-cause mortality among patients with septic shock – subgroup assessed regarding mortality after 28 days (follow-up after 28 days)												
4	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/717 (30%)	381/1239 (30.8%) 33.7%	RR 0.96 (0.83 to 1.11)	12 fewer per 1,000 (from 52 fewer to 34 more) 13 fewer per 1,000 (from 57 fewer to 37 more)	Moderate	Critical
Effect of use of albumin versus crystalloid on all-cause mortality among patients with septic shock – mortality assessed after 90 days (follow-up after 90 days)												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	265/617 (42.9%)	478/1120 (42.7%) 42.6%	RR 0.89 (0.79 to 1)	47 fewer per 1,000 (from 90 fewer to 0 more) 47 fewer per 1,000 (from 89 fewer to 0 more)	Moderate	Critical
All-cause mortality at final follow-up according to different risks of bias – All-cause mortality at final follow-up in subgroup with low or unclear risk of bias												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	439/1216 (36.1%)	505/1245 (40.6%) 44.6%	RR 0.9 (0.82 to 0.99)	41 fewer per 1,000 (from 4 fewer to 73 fewer) 45 fewer per 1,000 (from 4 fewer to 80 fewer)	High	Critical
All-cause mortality at final follow-up according to different risks of bias – All-cause mortality at final follow-up in subgroup with high risk of bias												
2	no methodology chosen					none	27/66 (40.9%)	200/561 (35.7%) 55.2%	RR 1.03 (0.75 to 1.42)	11 more per 1,000 (from 89 fewer to 150 more) 17 more per 1,000 (from 138 fewer to 232 more)	High	Critical

All-cause mortality at final follow-up after use of different concentrations of albumin, compared with crystalloid

Meta-analysis

Compared with crystalloids, low concentrations of albumin (4%-5%)[18-20] were not found to have reduced all-cause mortality at the final follow-up (RR: 0.96; 95% CI: 0.78-1.18; P = 0.68; I^2 = 8%). The high concentration (20%) albumin subgroups[14,21] were found to have slightly reduced all-cause mortality (RR: 0.88, 95% CI: 0.79-0.99, P = 0.03; I^2 = 0%) (**Figure 6**).

TSA

A diversity-adjusted information size of 3,177 patients was calculated using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%), D2 = 0%, an anticipated RR of 12.0% (**Table 3**) and an event proportion of 40.2% in the control arm (**Table 3**). The cumulative z curve was constructed using a random-effects model. TSA showed that, out of the required 3,177 patient sample size, only a sample size of 1,913 was accrued. The cumulative z curve touched the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit (**Figure 7**). This outcome indicates that the result was possibly a false positive because the required sample size was not met.

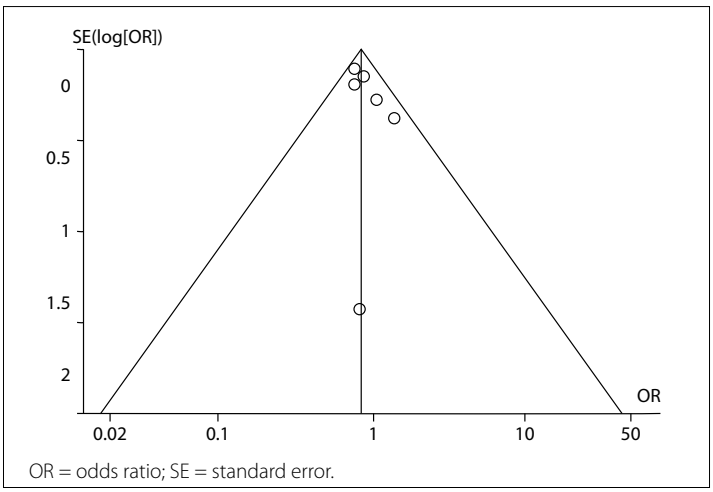

Figure 1. Publication bias was evaluated using a funnel plot.

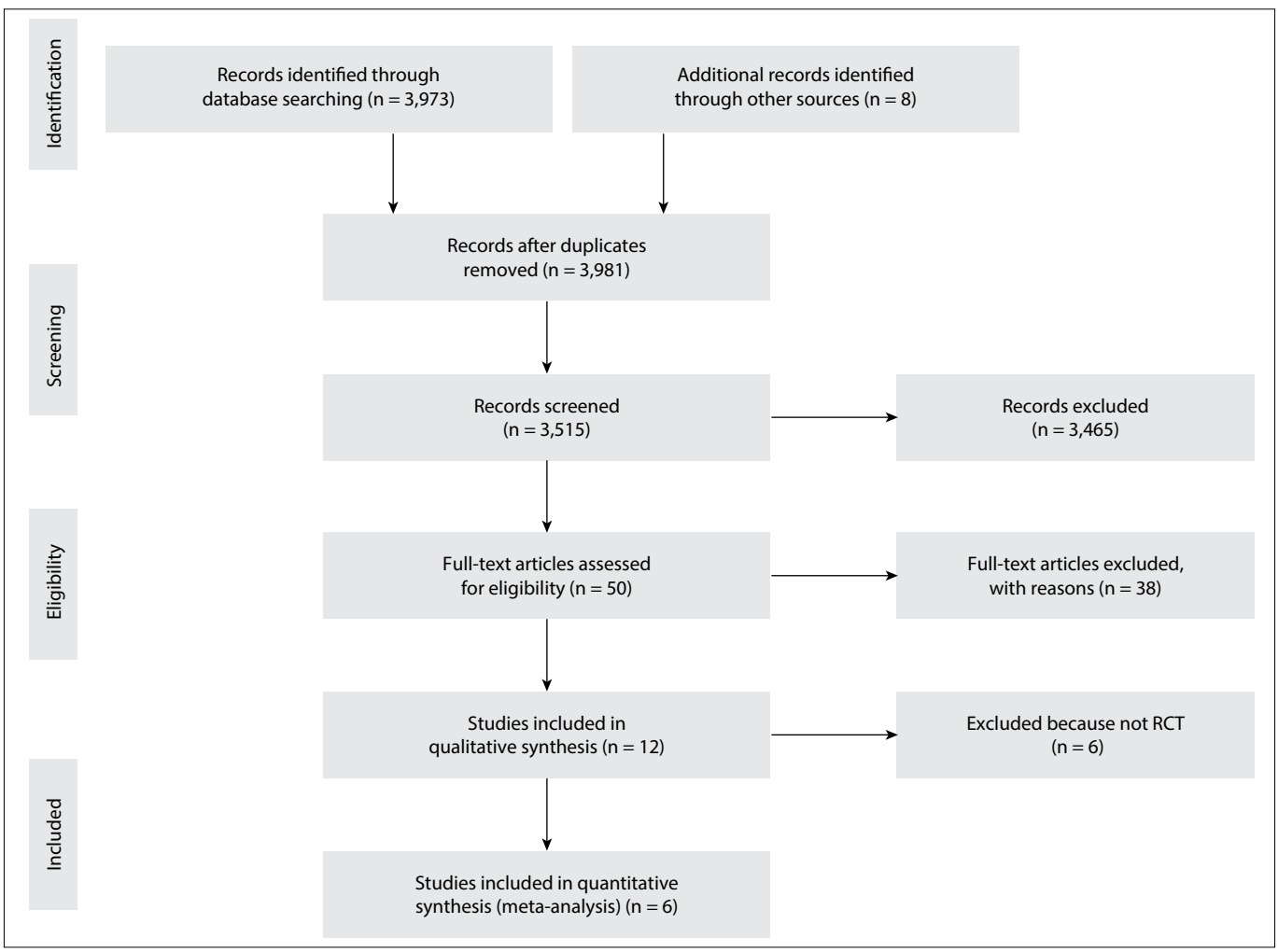

Figure 2. Flow chart of study selection.

Funnel plots for the comparisons of human albumin with crystalloid showed that there was no publication bias. The odds ratio (OR) and its standard error (SE) are plotted in **Figure 1**.

DISCUSSION

The purpose of this research was to compare the effects of albumin and crystalloid solution on the mortality rate among patients with septic shock. Meta-analysis for all-cause mortality showed that albumin offered no benefit in comparison with other interventions for septic shock patients at the final follow-up (P = 0.05). Through the subgroup analysis, significant benefits were observed for the subgroup of 20% albumin (P = 0.03). However, after conducting TSA on this meta-analysis we found that these results may not be definitive. Because the required information sizes were not reached, and because the cumulative z scores did not reach the trial sequential monitoring boundaries of benefit (**Figure 5**, **Figure 7**), these results indicated that albumin was not beneficial or harmful in these groups or subgroups. The initial meta-analysis results may have been false negative or positive outcomes. Therefore, additional high-quality RCTs are recommended in order to ensure that correct conclusions are reached. The main difference between the present analysis and previous studies is that, along with inclusion of the most recent RCTs,[14,18] a TSA was included in the analysis to confirm the results from the initial meta-analysis.

Table 4. Characteristics of studies included

Study name	Year	Country	Centers	Albumin concentration	Type of crystalloid	28-day mortality (albumin group)	28-day mortality (crystalloid group)	90-day mortality (albumin group)	90-day mortality (crystalloid group)	Final follow-up (albumin group)	Final follow-up (crystalloid group)
Rackow et al.[19]	1983	USA	1	5%	Normal saline	N/A*	N/A	N/A	N/A	5/7	3/4
SAFE study[20]	2004, 2011	Australia and New Zealand	16	4%	Normal saline	70/209	90/229	N/A	N/A	70/209	90/229
EARSS study[14]	2011	France	29	20%	Normal saline	96/399	103/393	N/A	N/A	96/399	103/393
CRYSTAL study[21]	2013	France, Belgium, Canada, Algeria and Tunisia	57	5% or 20%	Normal saline	19/59	157/557	22/59	197/557	22/59	197/557
ALBIOS study[15]	2014	Italy	100	20%	Crystalloid	N/A	N/A	243/558	281/563	243/558	281/563
RASP study[18]	2015	Brazil	1	4%	Lactated Ringer	30/50**	31/60**	N/A	N/A	30/50	31/60

*N/A = not applicable; **we assumed that 30 days was roughly equivalent to 28 days in the RASP study.

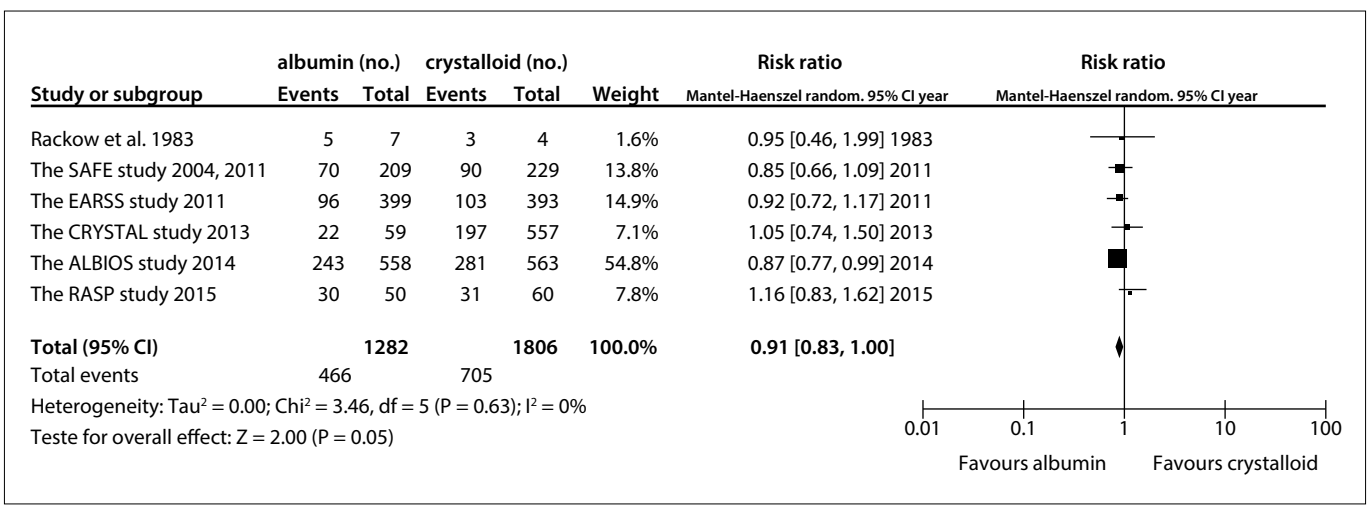

Figure 3. All-cause mortality ascertained at final follow-up, after use of albumin, compared with crystalloid.

As is well known, sample sizes need to be estimated such that clinical trials are repeatable and sufficient statistical power is ensured. In systematic reviews and meta-analyses, when the number of trials included or the total sample size is too small, the effect will be exaggerated due to random errors. TSA is a newly proposed statistical analysis method that can improve the strength and accuracy of meta-analyses through applying an overall quantity analysis to it. Duplication of a statistically significant experiment would increase the risk of type I error in the hypothesis test, which would mean creation of a false positive.[26-29] TSA[30] involves the principle and method of the trial sequence. Through checking the P-value and its CI, this method has the following significant advantages:

1. the conclusion can be generated earlier without increasing the type I error;
2. the sample size can be estimated; and
3. hints for further research studies are provided through numerical data and visualized sample sizes.

Research studies have shown that 25% of traditional meta-analyses produced false positive results due to small sample sizes.[31] With the help of this advanced method, our research was more precise and novel.

From a theoretical point of view, albumin is an ideal resuscitation fluid for treating septic shock, but its use in research studies has not demonstrated it to be superior to other resuscitation fluids. The reason for this discrepancy may have been the insignificant reduction in the mortality rate when albumin was compared with crystalloids and the lack of high-quality RCTs comparing albumin and crystalloid solutions in septic shock cases. In addition, further suggestions were provided for the experimental design of further studies based on the present research. More benefits could be produced through using crystalloid solutions compared with albumin, especially at high albumin concentrations, as well as through well-designed RCTs.

There are other limitations to the present research study. Firstly, a measurable error is generated if a blinded method was not applied in

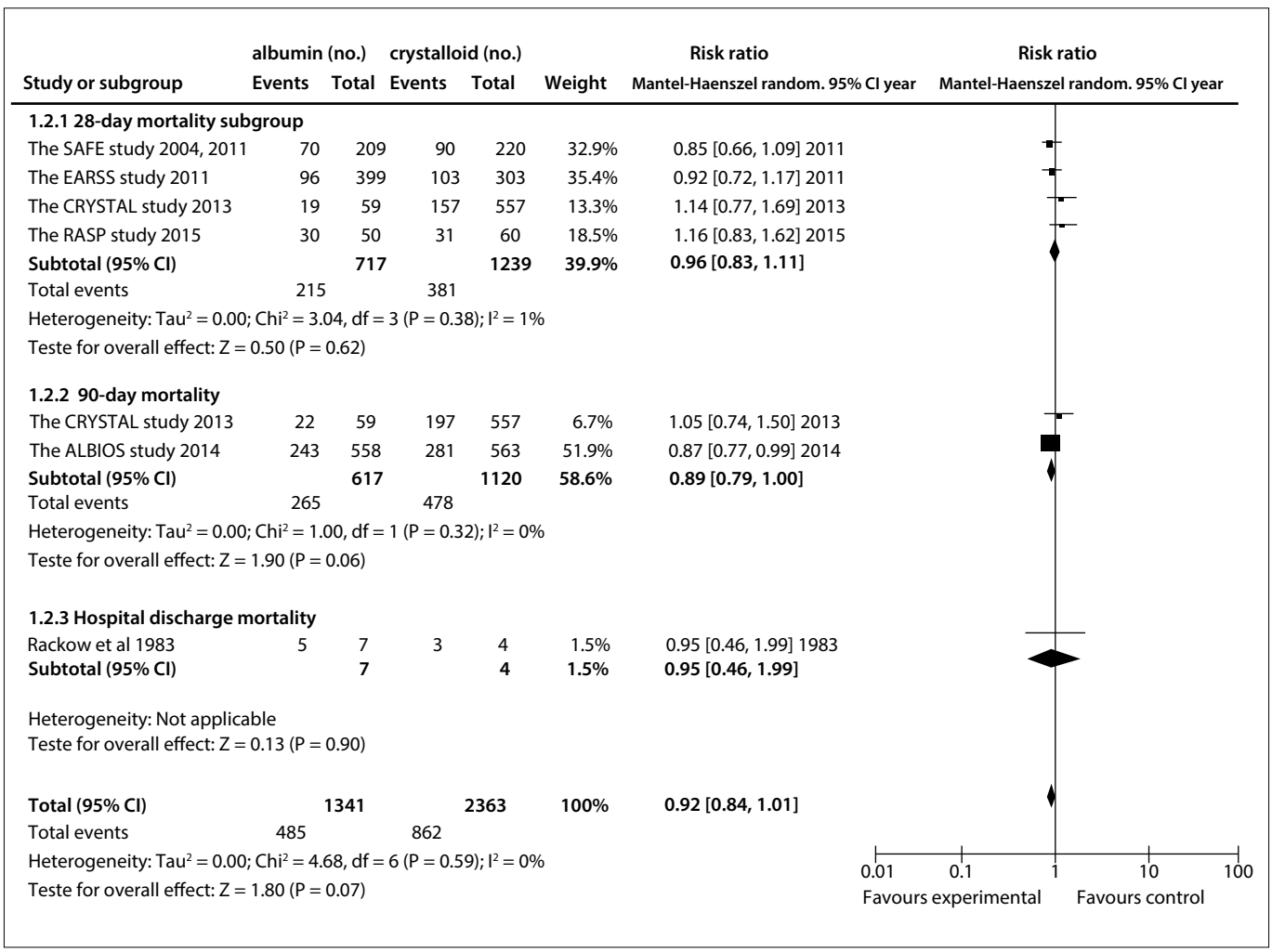

Figure 4. All-cause mortality ascertained at different follow-ups, after use of albumin, compared with crystalloid.

the studies, and therefore it is recommended that a blinded method should be used in future research studies for better quality. Secondly, although statistical heterogeneity between studies was not found, clinical and methodological heterogeneity may have been present. Thirdly, different follow-up durations were used, and different follow-up durations would obviously have different results. Fourthly, TSA had limitations, given that it was unable to resolve the error that was generated by the quality of the initial search methodology and by the uncertainty from the result. In addition, the initial search would have affected the TSA output if its quality was low.

Although TSA showed that there was a possibility that, without inclusion of further RCTs to provide additional support, the results from the meta-analysis could have been false positives, the output from the meta-analysis was still useful as guidance for experimental designs and field applications in the future. As the results showed, there is a high possibility that a high concentration of albumin can produce a positive result regarding decreased mortality, when used for fluid resuscitation in cases of septic shock. In short, TSA should be strongly recommended and should be more used for future review studies, so that evidence of greater reliability and consistency can be obtained.

PRECISE (NCT0019416)[9] has been completed. This is another large-scale RCT that focuses on comparing the effects of albumin

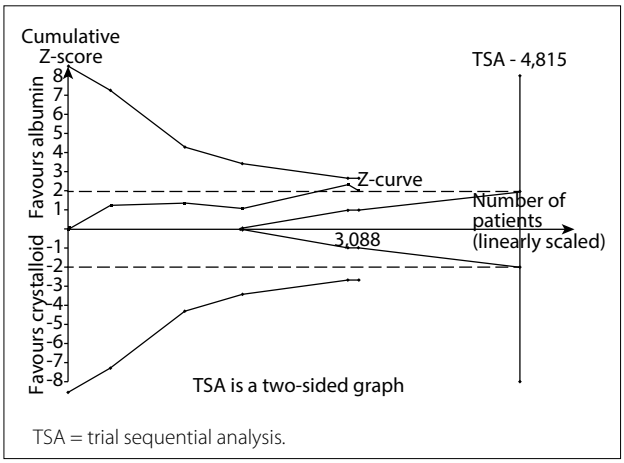

Figure 5. A diversity-adjusted information size of 4,815 patients was calculated using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%), D2 = 0%, an anticipated relative risk of 10.0% (refer to our meta-analysis) and an event proportion of 39% in the control arm (refer to our meta-analysis). The cumulative z curve was constructed using a random-effects model. Trial sequential analysis showed that 3,088 patients out of the required information size of 4,815 patients were accrued. The cumulative z curve touched the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit.

Study or subgroup	albumin (no.) Events	Total	crystalloid (no.) Events	Total	Weight	Risk ratio Mantel-Haenszel random. 95% CI year
1.3.1 Hypooncotic (4-5% albumin) subgroup						
Rackow et al 1983	5	7	3	4	6.9%	0.95 [0.46, 1.99] 1983
The SAFE study 2011	70	209	90	229	59.6%	0.85 [0.66, 1.09] 2011
The RASP study 2015	30	50	31	60	33.5%	1.16 [0.83, 1.62] 2015
Subtotal (95% CI)		**266**		**293**	**100.0%**	**0.96 [0.78, 1.18]**
Total events	105		124			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.18$, df = 2 (P = 0.34); $I^2 = 8\%$						
Teste for overall effect: Z = 0.41 (P = 0.68)						
1.3.2 Hyperoncotic (20% albumin)						
The EARSS study 2011	96	399	103	393	21.4%	0.92 [0.72, 1.17] 2011
The ALBIOS study 2014	243	558	281	563	78.6%	0.87 [0.77, 0.99] 2014
Subtotal (95% CI)		**957**		**956**	**100.0%**	**0.88 [0.79, 0.99]**
Total events	339		384			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$						
Teste for overall effect: Z = 2.21 (P = 0.03)						
1.3.3 Mix (5% or 20% albumin)						
The CRYSTAL study 2013	22	59	197	557	100.0%	1.05 [0.74, 1.50] 2013
Subtotal (95% CI)		**59**		**557**	**100.0%**	**1.05 [0.74, 1.50]**
Total events	22		197			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.77)						

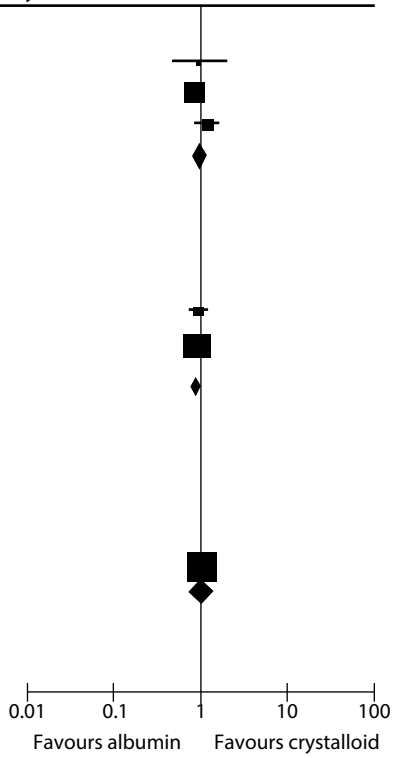

Figure 6. All-cause mortality ascertained at final follow-up, after use of different albumin concentrations, compared with crystalloid.

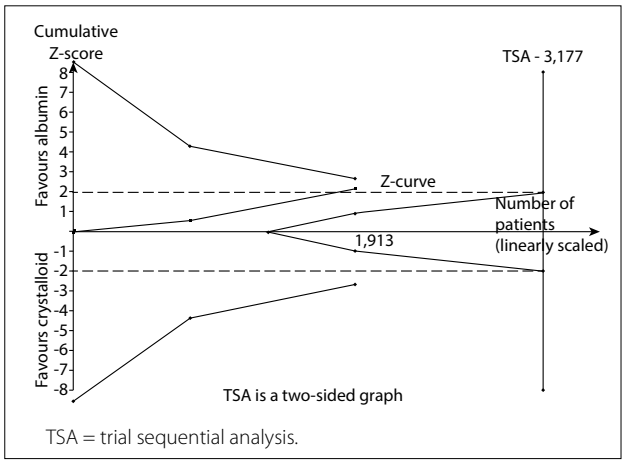

Figure 7. A diversity-adjusted information size of 3,177 patients was calculated using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%), D2 = 0%, an anticipated relative risk of 12.0% (refer to our meta-analysis) and an event proportion of 40.2% in the control arm (refer to our meta-analysis). The cumulative z curve was constructed using a random-effects model. Trial sequential analysis showed that 1,913 patients out of the required information size of 3,177 patients were accrued. The cumulative z curve touched the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit.

and normal saline on the mortality rate due to septic shock. The conclusion of this RCT is eagerly awaited, given that the sample size of the meta-analysis will reach the required information size. Thus, it will help determine whether the reduction in mortality that is associated with use of albumin is a truly positive result or a type I error.

CONCLUSIONS

The results from the meta-analysis showed that, in comparison with use of crystalloid, human albumin did not decrease all-cause mortality, as evaluated at the final follow-up. The trial sequential analysis results suggest that the negative results observed so far might not be definitive. Further RCTs are needed to confirm this result.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10. PMID: 26903338; doi: 10.1001/jama.2016.0287.
2. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583-93. PMID: 24635770; doi: 10.1056/NEJMoa1312173.
3. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51. PMID: 23984731; doi: 10.1056/NEJMra1208623.
4. Ospina-Tascon G, Neves AP, Occhipinti G, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med. 2010;36(6):949-55. PMID: 20221744; doi: 10.1007/s00134-010-1843-3.
5. Niemi TT, Miyashita R, Yamakage M. Colloid solutions: a clinical update. J Anesth. 2010;24(6):913-25. PMID: 20953964; doi: 10.1007/s00540-010-1034-y.
6. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901-11. PMID: 23075127; doi: 10.1056/NEJMoa1209759.
7. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethyl starch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16(3):R94. PMID: 22624531; doi: 10.1186/cc11358.
8. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124-34. PMID: 22738085; doi: 10.1056/NEJMoa1204242.
9. McIntyre L, Fergusson DA, Rowe B, et al. The PRECISE RCT: evolution of an early septic shock fluid resuscitation trial. Transfus Med Rev. 2012;26(4): 333-41. PMID: 22222146; doi: 10.1016/j.tmrv.2011.11.003.
10. Zhong JZ, Wei D, Pan HF, et al. Colloid solutions for fluid resuscitation in patients with sepsis: systematic review of randomized controlled trials. J Emerg Med. 2013;45(4):485-95. PMID: 23932700; doi: 10.1016/j.jemermed.2013.05.018.
11. Jiang L, Jiang S, Zhang M, Zheng Z, Ma Y. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. PLOS One. 2014;9(12):e114666. PMID: 25474401; doi: 10.1371/journal.pone.0114666.
12. Ma PL, Peng XX, Du B, et al. Sources of heterogeneity in trials reporting hydroxyethyl starch 130/0.4 or 0.42 associated excess mortality in septic patients: A systematic review and meta-regression. Chin Med J (Engl). 2015;128(17):2374-82. PMID: 26315087; doi: 10.4103/0366-6999.163387.
13. Raghunathan K, Bonavia A, Nathanson BH, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. Anesthesiology. 2015; 123(6): 1385-93. PMID: 26414499; doi: 10.1097 /ALN. 0000000000000861.
14. Charpentier J, Mira JP, EARSS Study Group. Efficacy and tolerance of hyperoncotic albumin administration in septic shock patients: the EARSS study (Abstract). Intensive Care Med. 2011; 37(Suppl1):S115.
15. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-21. PMID: 24635772; doi: 10.1056/NEJMoa1305727.
16. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ. 2014;349:g4561. PMID: 25099709; doi: 10.1136/bmj.g4561.
17. Xu JY, Chen QH, Xie JF, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. Crit Care. 2014;18(6):702. PMID: 25499187; doi: 10.1186/s13054-014-0702-y.
18. Park C, Osawa E, Almeida J, et al. Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP) study: preliminary data of a randomized controlled trial. Crit Care. 2015;19(Suppl 1):P355. doi:10.1186/cc14435.

19. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med. 1983;11(11):839-50. PMID: 6194934.
20. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247-56. PMID: 15163774; doi: 10.1056/NEJMoa040232.
21. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809-17. PMID: 24108515; doi: 10.1001/jama.2013.280502.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41. PMID: 20171303; doi: 10.1016/j.ijsu.2010.02.007.
23. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011]. Cochrane Collaborations; 2011. Available from: http://handbook-5-1.cochrane.org/. Accessed in 2018 (Jan 3).
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. PMID: 18436948; doi: 10.1136/bmj.39489.470347.AD.
25. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-analysis. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors. Part 3: Fixed-effect versus random-effect models. West Sussex: John Wiley & Sons; 2009. p. 61-102. ISBN: 978-0-470-05724-7.
26. Wang JY, Xiao L, Chen J, et al. Potential effectiveness of traditional Chinese medicine for cardiac syndrome X (CSX): a systematic review and meta-analysis. BMC Complement Altern Med. 2013;13:62. PMID: 23497135; doi: 10.1186/1472-6882-13-62.
27. Wang HF, Yu JT, Tang SW, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry. 2015;86(2):135-43. PMID: 24828899; doi: 10.1136/jnnp-2014-307659.
28. Thorlund K, Engstr OM, Wetterslev J, et al. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research; 2017. Available from http://www.ctu.dk/tsa/files/tsa_manual.pdf. Accessed in 2018 (Mar 9).
29. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell; 2008. ISBN: 978-0-470-69951-5.
30. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol. 2008;61(1):64-75. PMID: 18083463; doi: 10.1016/j.jclinepi.2007.03.013.
31. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol. 2009;38(1):276-86. PMID: 18824467; doi: 10.1093/ije/dyn179.

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Supplementary file.

Studies excluded and reasons for this.

First author	Subject	Reason for exclusion
Dahn 1979[1]	Negative inotropic effect of albumin resuscitation for shock.	Seriously injured patients were included in the study, and data on severe sepsis were inadequate.
Lucas 1979[2]	Impaired salt and water excretion after albumin resuscitation for hypovolemic shock.	Hypovolemic shock patients were included in the study, and data on severe sepsis were inadequate.
Lucas 1980[3]	Impaired pulmonary function after albumin resuscitation from shock.	Shock patients were included in the study, and data on severe sepsis were inadequate.
Brown 1988[4]	Effect of albumin supplementation during parenteral nutrition on hospital morbidity.	Patients requiring central total parenteral nutrition were included in the study, and data on severe sepsis were inadequate.
Foley 1990[5]	Albumin supplementation in critically ill patients.	Hypoalbuminemic patients were included in the study, and data on severe sepsis were inadequate.
Younes 1992[6]	Hypertonic solutions for treating hypovolemic shock: a prospective, randomized study on patients admitted to the emergency room.	Hypovolemic shock patients were included in the study, and data on severe sepsis were inadequate.
Stockwell 1992[7]	Colloid solutions in critically ill patients: a randomized comparison of albumin and polygeline. Outcome and duration of stay in the intensive care unit.	All patients were included in the study, and data on severe sepsis were inadequate.
Tuchschmidt 1992[8]	Elevation of cardiac output and oxygen delivery for improvement of outcomes in septic shock cases.	Septic shock patients were treated using an algorithm to increase confidence intervals to a different level.
Golub 1994[9]	Efficacy of albumin supplementation in surgical intensive care unit: a prospective, randomized study.	The study was conducted in the surgical intensive care unit, and data on severe sepsis were inadequate.
Steltzer 1994[10]	Hemodynamic evaluation during small-volume resuscitation among patients with acute respiratory failure.	Acute respiratory failure patients were included in the study, and data on severe sepsis were inadequate.
Boldt 1996[11]	Effects of albumin versus hydroxyethyl starch solution on cardio respiratory and circulatory variables in critically ill patients.	Comparison was between albumin and low-molecular weight hydroxyethyl starch solution, not between albumin and crystalloid.
Rock 1997[12]	Pentastarch instead of albumin as replacement fluid for therapeutic plasma exchange.	Comparison was between albumin and pentastarch, not between albumin and crystalloid.
Rubin 1997[13]	Randomized, double blind study on intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition.	Hypoalbuminemic patients were included in the study, and data on severe sepsis were inadequate.
Ernest 1999[14]	Distribution of normal saline and 5% albumin infusions among septic patients.	Septic patients were included in the study, and data on severe sepsis were inadequate.
Wu 2001[15]	Hemodynamic response of modified fluid gelatin compared with lactated Ringer's solution for volume expansion in emergency resuscitation of hypovolemic shock patients: preliminary report on a prospective, randomized trial.	Hypovolemic shock patients were included in the study, and data on severe sepsis were inadequate.
Oliveira 2002[16]	Acute hemodynamic effects of a hypertonic saline/dextran solution in stable patients with severe sepsis.	Comparison was between hypertonic saline/dextran solution and saline, not between albumin and crystalloid.
Quinlan 2004[17]	Albumin influenced total plasma antioxidant capacity favorably in patients with acute lung injury.	Acute lung injury patients were included in the study, and data on severe sepsis were inadequate.
Veneman 2004[18]	Human albumin and starch administration in critically ill patients: a prospective randomized clinical trial.	Severe sepsis patients were included in the study, and the mortality data on the albumin group and crystalloid group were inadequate.
Vincent 2005[19]	Albumin administration in acutely ill patients in relation to increased mortality :results from the SOAP study.	Not a randomized controlled or parallel clinical trial.
Palumbo 2006[20]	Effects of hydroxyethyl starch solution on critically ill patients.	Comparison was between albumin and hydroxyethyl starch, not between albumin and crystalloid.
Dubois 2006[12]	Albumin administration improved organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study.	Hypoalbuminemic patients were included in the study, and data on severe sepsis were inadequate.
Bellomo 2006[22]	Effects of saline or albumin resuscitation on acid-base status and serum electrolytes.	Not a randomized controlled or parallel clinical trial.
McIntyre 2007[23]	Resuscitating patients with early severe sepsis: a Canadian multicenter observational study.	Not a randomized controlled or parallel clinical trial.
Guidet 2007[24]	The COASST study: cost-effectiveness of albumin in cases of severe sepsis and septic shock.	Not a randomized controlled or parallel clinical trial.
McIntyre 2008[25]	Fluid resuscitation in management of early septic shock (FINESS): a randomized controlled feasibility trial.	Comparison was between pentastarch and saline, not between albumin and crystalloid.

Continue...

Supplementary file.

Studies excluded and reasons for this (continuation).

First author	Subject	Reason for exclusion
Friedman 2008[26]	Hemodynamic effects of 6% and 10% hydroxyethyl starch solutions versus 4% albumin solution in septic patients.	Comparison was between hydroxyethyl starch and albumin, not between albumin and crystalloid.
Schortgen 2008[27]	Risk associated with hyperoncotic colloids in patients with shock.	Not a randomized controlled or parallel clinical trial.
Dolecek 2009[28]	Therapeutic influence of 20% albumin versus 6% hydroxyethyl starch on extravascular lung water in septic patients: a randomized controlled trial.	Comparison was between hydroxyethyl starch and albumin, not between albumin and crystalloid.
Bellomo 2009[29]	Effects of saline or albumin resuscitation on standard coagulation tests.	Not a randomized controlled or parallel clinical trial.
van der Heijden 2009[30]	Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and non-septic critically ill patients with hypovolemia.	Hypovolemic septic patients were included in the study, and the mortality data on the albumin group and crystalloid group were inadequate.
Trof 2010[31]	Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolemia.	Critically ill septic patients were included in the study, and the mortality data on the albumin group and crystalloid group were inadequate.
Finfer 2010[32]	Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units.	Not a randomized controlled or parallel clinical trial.
Zhu 2011[33]	Hypertonic saline and hydroxyethyl starch for treating severe sepsis.	Comparison was between hypertonic saline and hydroxyethyl starch, not between albumin and crystalloid.
Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee 2011[34]	Crystalloid versus hydroxyethyl starch trial: protocol for a multicenter randomized controlled trial on fluid resuscitation with 6% hydroxyl starch (130/0.4) compared with 0.9% sodium chloride (saline) in intensive care patients, regarding mortality.	Comparison was between crystalloid and hydroxyethyl starch, not between albumin and crystalloid.
Scandinavian Critical Care Trials Group 2011[35]	Comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis (6S: Scandinavian Starch for Severe Sepsis/Septic Shock trial): study protocol, design and rationale for a double-blinded, randomized clinical trial.	Comparison was between crystalloid and hydroxyethyl starch, not between albumin and crystalloid.
McIntyre 2012[36]	Fluid resuscitation with 5% albumin versus normal saline in early septic shock: a pilot randomized, controlled trial.	Septic shock patients were included in the study, and the mortality data on the albumin group and saline group were inadequate.
van Haren 2012[37]	Hypertonic fluid administration in patients with septic shock: a prospective randomized controlled pilot study.	Comparison was between hypertonic fluid and isotonic fluid, not between albumin and crystalloid.
Myburgh 2012[38]	Hydroxyethyl starch or saline for fluid resuscitation in intensive care.	Comparison was between hydroxyethyl starch and saline, not between albumin and crystalloid.
Yunos 2012[39]	Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults.	Not a randomized controlled or parallel clinical trial
McIntyre 2012[40]	The PRECISE RCT: evolution of an early septic shock fluid resuscitation trial.	Septic shock patients were included in the study, and the mortality data on the albumin group and saline group were inadequate.
Perez 2013[41]	Intravenous 0.9% sodium chloride therapy did not reduce length of stay of alcohol-intoxicated patients in the emergency department: a randomized controlled trial.	Acute alcohol intoxication patients were included in the study; the mortality data on the albumin group and saline group were inadequate; and the comparison was not between albumin and crystalloid.
Masson 2014[42]	Presepsin (soluble CD14 subtype) and procalciton in levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial.	Comparison was not between albumin and crystalloid.
Caironi 2015[43]	Albumin in critically ill patients: the ideal colloid?	Not a controlled or parallel clinical trial.
Chang 2016[44]	Choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock.	Choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock.

Cost of a community mental health service: a retrospective study on a psychosocial care center for alcohol and drug users in São Paulo

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KEY WORDS:
Substance-related disorders.
Community mental health services.
Costs and cost analysis.
Direct service costs.
Substance abuse treatment centers.

ABSTRACT

BACKGROUND: Psychosocial care centers for alcohol and drug users (CAPS-ad) are reference services for treatment of drug users within the Brazilian National Health System. Knowledge of their total costs within the evidence-based decision-making process for public-resource allocation is essential. The aims here were to estimate the total costs of a CAPS-ad and the costs of packages of care (according to intensity of care); to ascertain the ratio between total CAPS-ad costs and the federal funding allocated; and to describe the methods for estimating unit costs for each CAPS-ad cost component.

DESIGN AND SETTING: Retrospective study conducted in a public community mental health service.

METHODS: This was a retrospective cost description study on a CAPS-ad located in a city in the state of São Paulo, using a public healthcare provider perspective and a top-down approach, conducted over a 180-day period from March 1 to August 30, 2015.

RESULTS: The total mean monthly costs of the CAPS-ad were BRL 64,017.54. Healthcare staff accounted for 56.5% of total costs. The mean costs per capita and per month for intensive and non-intensive care packages were, respectively, BRL 668.34 and BRL 37.12.

CONCLUSIONS: The federal budget allocation covered 62.1% of the CAPS-ad costs and the remaining 37.9% end up funded by the municipal government. The cost of the intensive package of care was 18 times greater than the non-intensive package. Developing criteria for using services and different packages of care based on patients' needs, and optimizing human resources according to specific actions, may improve people's mental health and avoid wasted resources.

INTRODUCTION

Substance-related disorders have been a priority of the Brazilian public health agenda since the beginning of the last decade, when the federal government established specific policies and programs,[1] such as the Psychosocial Care Network (RAPS). This priority agenda is based on the prevalence of drug and alcohol use in Brazil, and on their consequences for users and society.[2-4] The main care strategy for treating substance-related disorders within RAPS comprises community-based mental health services (CMHS), known as psychosocial care centers for alcohol and drug users (CAPS-ad). Knowledge of their costs within the decision-making process for allocation of public resources is essential.

Brazil is a country of huge territorial extent, but 50% of the Brazilian population is concentrated in only 5% of its municipalities.[1] This characteristic has justified regionalization of this country's healthcare management, and the three levels of government (federation, states and municipalities) are expected to agree on the management and costing of healthcare services. The CAPS-ad system is partially funded by the national government, but so far there is no information regarding whether the federal funding entirely covers the costs of CAPS-ad, and what the budget impact on municipalities would be, in relation to implementing and maintaining these services.

The territorial complexities of Brazil, along with the need to expand mental health care coverage for people with substance-related disorders, highlight the need for economic planning through cost studies and economic evaluations.[5] Very few economic studies have examined psychosocial interventions for people with substance-related disorders in low and middle-income countries.[6] This was corroborated by our finding from the literature, while conducting this study, that no cost studies on CAPS-ad have been undertaken. Data on CAPS-ad costs would provide support

for the decision-making process regarding opening new services of this nature, through helping healthcare managers to analyze the feasibility of maintaining such services over time.

The main aim of this study was to estimate the total costs of a CAPS-ad that is located in a city in the state of São Paulo, and the costs of three packages of care (intensive, semi-intensive and non-intensive) delivered by this service for patients with substance-related disorders, from the public healthcare provider perspective. The additional objectives were to ascertain the ratio between total CAPS costs and the federal funding allocated to this service and to describe the methods for estimating the unit costs for each CAPS cost component.

METHODS

This was a cross-sectional study that was conducted to estimate the total costs of a CAPS-ad located in the city of Rio Claro, state of São Paulo, covering a 180-day period from March 1 to August 30, 2015. Data on costs were extracted from the municipal accounting database and a top-down approach was applied for the cost estimation. The CAPS-ad costs were estimated for a 180-day period in the year 2015 and then the ratio between costs funded by the federal and municipal governments was examined. The 180-day period was chosen because this provided the best data quality in the administrative database that was made available by the municipal government. This study adopted the perspective of the public healthcare provider because there are no national or regional published data on the unit costs and cost components of this kind of service in Brazil.

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP), under protocol number 0296/15.

Service description: psychosocial care center for alcohol and drug users (CAPS-ad)

A CAPS-ad is a community-based mental health service that promotes public comprehensive care for people with substance-related disorder. The CAPS-ad that was studied here covers a population of approximately 215,960 people. It welcomes spontaneous and referred demand, is integrated with primary care and psychiatric and general hospitals for acute inpatient hospitalizations. This service is one of five that, together, make up the municipal mental health setting: another two CAPS, of which one deals with all mental disorders and is open 24 hours per day and the other deals with children and adolescents; and two outpatient services. The service that is the focus of the present study offers treatment through three types of package of care: intensive, semi-intensive and non-intensive.

Individuals with severe use of drugs are generally directed towards the intensive package of care. The semi-intensive package of care is for individuals who seek the service presenting moderate use of drugs that puts them at risk of greater worsening of their functioning; or those who migrate to an intermediate treatment after showing improvements through intensive treatment. The non-intensive package of care offers support for users who have good social and family ties, those who make moderate or severe use of drugs but who work and can only attend the service at specific times, or those who are in the process of leaving the service because they have presented improvements.

Estimation of cost components

The following CAPS-ad cost component categories were considered: *Healthcare staff costs*: These were the costs of healthcare professionals working at this center, including two psychiatrists, one general practitioner, one nurse, two nursing technicians, two psychologists, two occupational therapists and one social worker. Firstly, their total costs over a 180-day period were estimated. Secondly, unit costs were determined. Lastly, the costs for each healthcare staff intervention within the care packages were estimated.

Medication costs: These were categorized as the costs of psychotropic and non-psychotropic medications. Firstly, the per capita monthly costs of medication consumption were obtained. Secondly, the per capita monthly costs were extrapolated to the 180-day period, considering the mean number of patients assisted by the service over this period (810 patients). Then, the unit costs were defined.

Revenue costs: These were the costs of support services (diet service: lunch and snacks), utilities (expenses with electricity, telephone and gas consumption), consumables (medical supplies, catering, stationery and cleaning supplies), non-healthcare human resources (security, which was provided through an outsourced hired service hired; and cleaning services, consisting of one cleaning professional) and overheads (healthcare manager, one assistant and one receptionist). Their costs were estimated considering the number of working hours and salaries.

Capital costs: These consisted of rent, equipment and building repair. Equipment costs were adjusted according to the consumer price index by using the market price for 2015 (presented as **Supplementary Table S1**). The unit costs were extracted from three online stores in September 2015. Then, these costs were annuitized by estimating the equivalent annual annuity (EAA), with a 5% discount factor (standard in Brazil), and by taking the lifetime use of equipment to be five years, as can be seen in Drummond et al.[7]

CAPS-ad funding sources

It is expected that CAPS-ad will be funded from federal, state and municipal public healthcare budgets (**Figure 1**). The federal

healthcare budget is allocated to the state and municipal governments through six funding packages, of which two are oriented towards CAPS-ad: the *Medication* funding package (arrow 1) and the *Medium and High-Complexity* healthcare funding package (arrow 2).[8] The *Medication* funding package is firstly allocated to the state government for drug purchasing.

The *Medium and High Complexity* healthcare funding is allocated directly to the municipal healthcare budget to fund CAPS-ad and other healthcare services. In 2015, the federal government released Brazilian reais (BRL) 39,780.00 per month to fund each CAPS-ad within the national territory, and the municipal healthcare budget funded the remaining costs, which were not publicly known until the analysis of the present study. In **Figure 1**, arrows 3 and 4 respectively represent the federal government budget allocated to municipal government and the municipality's own healthcare budget, which were both used to fund CAPS-ad.

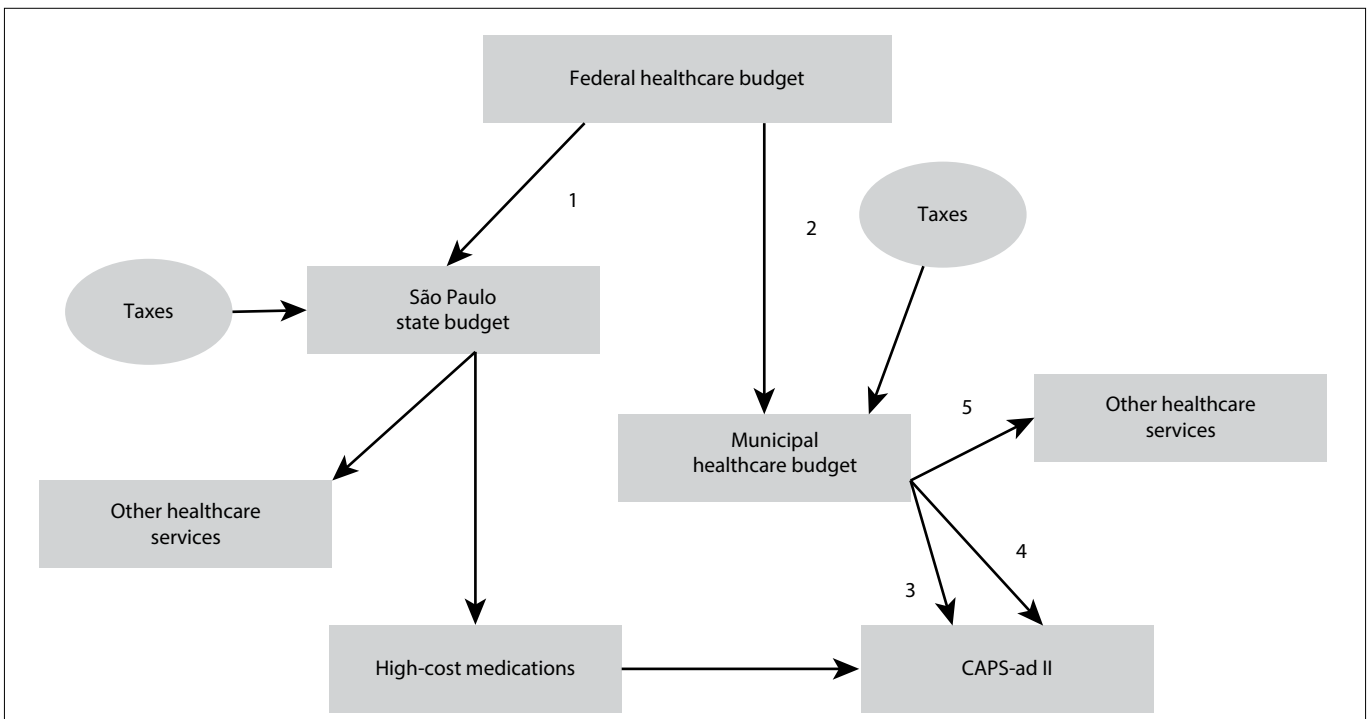
Cost components: packages of care

The *intensive package of care* (IPC) offered support from Monday to Friday, from 8 am to 5 pm in this CAP-ad. This one-month package included: one visit to a psychiatrist, one visit to a general practitioner, 12 group sessions with an occupational therapist, 12 group sessions with a psychologist, 10 group sessions with a social worker, six group sessions with a nurse, 20 individual routine nursing care sessions and eight individual sessions with a health case manager, approximately. One visit to a psychiatrist or general practitioner was estimated to last for 30 minutes. The group sessions were considered to last 90 minutes and each session was expected to cater for a mean of 10 patients per session. An individual session was estimated to last for 60 minutes, and an individual routine care session with an assistant nurse care was estimated to last for 15 minutes. The *health case manager* could be an occupational therapist, a nurse, a social worker or a psychologist, and their individual sessions were estimated to last for 60 minutes.

The *semi-intensive package of care* (SIPC) was delivered on three days a week. This one-month package included: one visit to a psychiatrist, one visit to a general practitioner, eight group sessions with an occupational therapist, eight group sessions with a psychologist, four group sessions with a social worker, four group sessions with a nurse, 12 individual routine care sessions with a nurse and four individual sessions with a health case manager, following the same patterns of length as mentioned previously.

Patients attending the IPC and the SIPC sessions received three meals per day during the treatment: breakfast, lunch and afternoon snacks.

The one-month *non-intensive package of care* (NIPC) included one visit to a psychiatrist and one weekly group session with a health case manager. Meals were not included in this package.



Brasil. Ministério da Saúde. Pactos pela Vida, em Defesa do SUS e de Gestão. Adapted from an official document.[8]

Figure 1. Funding sources for Psychosocial Care Centers for Alcohol and Drug Users in Brazil.

Analyses

Descriptive analyses on cost distributions were carried out for each cost component. Unit costs were calculated by means of a top-down approach, and unit costs for each mental health intervention per individual were estimated, considering the average length of one visit and one-tenth of the costs of a group session. The ratio between funding sources was obtained by calculating the cost difference between the total CAPS costs and the federal government funding. Sensitivity analysis was carried out both on the total costs of the CAPS-ad and on the total costs of the packages of care, in order to enable transferability of the study results to other Brazilian regions. Regarding the total costs of the CAPS-ad, a 15% cost variation in healthcare staff costs (rate established in accordance with the mean salary variation among the Brazilian regions in relation to the average salary of workers in the southeastern region)[9] and a 30% variation in the costs of rent,[10] revenue, medications and maintenance/repairs upwards (worst scenario) and downwards (best scenario) were considered. Lastly, in relation to the packages of care, two distinct scenarios were considered for the group sessions, with five participants (worst scenario) and 15 participants (best scenario) per session, especially because there are large variations in the numbers of participants in group sessions in the real context of mental health services.

RESULTS

Table 1 shows the unit costs per mental health professional and the total cost per professional category for the 180-day period. The healthcare staff cost was BRL 216,918.00 over this period, which was equivalent to USD 68,213.20 after conversion using purchasing parity power (PPP) exchange rates relating to 2015.[11]

The mental health treatments offered by the CAPS-ad and their respective costs are described in **Table 2**.

Table 3 shows the total revenue and total medication costs and their unit costs. The total revenue and total medication costs over the 180-day period were, respectively, BRL 93,425.72 (USD 29,379.15, using PPP) and BRL 66,058.04 (USD 20,772.96, using PPP).

Regarding capital costs over the 180-day period, the rent cost was BRL 6,826.68, or BRL 37.92 per day, and the maintenance/repair cost was BRL 125.50, or BRL 0.70 per day. The total cost of equipment was BRL 6,500.00, or BRL 750.67 over the 180-day period and BRL 4.17 per day. The total capital cost over the 180-day period was BRL 7,702.85 (USD 2,422.27, using PPP).

Considering healthcare staff, revenue, medications and capital costs, the CAPS-ad costs over the 180-day period were BRL 384,105.27, i.e. an average of BRL 64,017.54 or USD 20,131.54 (using PPP) per month. Healthcare staff accounted for 56.5% of the total CAPS-ad costs, revenue costs 24.3%, medication costs 17.2% and capital costs 2%. **Table 4** shows the sensitivity analysis

Table 1. Total costs and unit costs relating to healthcare staff in Brazilian reais (BRL)*

Cost components	Quantity	Worked hours over the 180-day period	Total costs in 180 days over the 180-day period, in BRL	Unit cost	Cost per unit BRL
Healthcare staff					
Psychiatrist	2	960	54,069.48	Hour	56.32
General practitioner	1	480	27,034.74	Hour	56.32
Occupational therapist	2	1,440	35,974.32	Hour	24.98
Psychologist	2	1,920	35,974.32	Hour	18.73
Social worker	1	720	19,040.70	Hour	26.44
Nurse	1	960	19,040.70	Hour	19.83
Assistant nurse	2	1,920	25,784.40	Hour	13.42
Total	**11**	**8,400**	**216,918.66**	-	-

*1 USD (United States dollars) = BRL 3.18 (using purchasing parity power exchange rate for 2015).[9]

Table 2. Unit costs for mental health treatment in Brazilian reais (BRL)

Healthcare staff	Description	Unit cost	Cost per capita, 2015
Visit to psychiatrist	Individual visit of 30 min	Visit	28.16
Visit to general practitioner	Individual visit of 30 min	Visit	28.16
Group session with occupational therapist	90-min group session, with an average of 10 patients	Session	3.74*
Group session with social worker	90-min group session, with an average of 10 patients	Session	3.96*
Group session with psychologist	90-min group session, with an average of 10 patients	Session	2.80*
Group session with nurse	90-min group session, with an average of 10 patients	Session	2.97*
Individual session with assistant nurse	15-min individual appointment	Appointment	3.35
Individual session with health case manager	60-min individual appointment	Appointment	22.49
Group session with health case manager	90-min group session, with an average of 10 patients	Session	2.24*

*Cost of one group session per patient.

results on the total CAPS-ad costs in the best and worst scenarios, compared with the total costs for the service.

In the same year, the federal funding allocated to the municipal government for financing the CAPS-ad was BRL 39,780.00 per month or BRL 238,680.00 (USD 75,056.60, using PPP) over the 180-day period.[12] In other words, federal funding covered 62.1% of the total CAPS-ad cost, and the municipal government funded the remaining 37.9%, or BRL 145,425.27 (USD 45,731.21, using PPP) over the 180-day period, and BRL 24,237.54 per month (USD 7,621.86, using PPP).

Over the 180-day period, the CAPS-ad offered assistance to approximately 810 patients. Thus, the mean monthly CAPS-ad treatment cost per capita was BRL 474.20 (USD 149.12, using PPP). BRL 294.47 was funded by the federal government and BRL 179.73 by the municipal government.

Data on the care packages are shown in **Table 5**. Based on the unit costs for mental health treatment at this CAPS-ad (**Table 2**), it was possible to estimate the cost of a one-month package of care per capita. Monthly, the IPC cost BRL 668.34 (USD 210.16, using PPP), the SIPC cost BRL 404.04 (USD 127.05) and the NIPC cost

Table 3. Total revenue and total medication costs in Brazilian reais (BRL)

Cost components	Total costs over 180-day period	Minimum cost per month	Maximum cost per month	Unit cost	Cost per unit
Revenue costs					
Support Services					
Diet - lunch	23,330.60	3,457.00	4,462.70	Per lunch	11.00
Diet - snacks	379.07	46.80	141.05	Per snack	0.23
Total	**23,709.67**	**3,503.80**	**4,603.75**	-	-
Non-health human resources					
Cleaner	9,129.42	-	-	Hour	9.50
Security	2.454.36	-	-	Hour	2.55
Total	**11,583.78**	**1,930.63**	**1,930.63**	-	-
Utilities					
Electricity	1,420.94	185.94	236.82	Day	7.89
Telephone	1,977.44	298.51	329.57	Day	11.00
Gas	47.00	0	47.00	Day	0.26
Total	**3,445.38**	**484.45**	**613.39**	-	-
Consumables	5,019.59	572.54	836.54	Day	27.89
Total	**5,019.59**	**572.54**	**836.54**	-	-
Overhead					
Healthcare manager	29,489.00	-	-	Hour	15.36
Receptionist	9,129.42	-	-	Hour	4.75
Secretary	11,048.88	-	-	Hour	5.75
Total	**49,667.30**	**8,277.88**	**8,277.88**	-	-
Total	**93,425.72**	**14,769.30**	**16,262.19**	-	-
Medication costs					
Psychotropic	46,209.80	-	-	Day	256.72
Non-psychotropic	19,848.24	-	-	Day	110.26
Total	**66,058.04**	-	-		

Table 4. Sensitivity analysis for total CAPS-ad costs in Brazilian reais (BRL)

	Base Cost	Best scenario				Worst scenario			
		(%)	Variation (BRL)	Cost (BRL)	Variation/base cost (BRL)	(%)	Variation (BRL)	Cost (BRL)	Variation/base cost (BRL)
Healthcare staff costs	216,918.66	-15.0	-32,537.80	184,380.86		+15.0	+32,537.80	249,456.46	
Revenue costs	93,425.72	-30.0	-28,027.72	65,398.00		+30.0	+28,027.72	121,453.44	
Medication costs	66,058.04	-30.0	-19,817.41	46,240.63		+30.0	+19,817.41	85,875.67	
Capital cost	7,702.85			7,342.00				7,582.57	
Equipment	6,500.00	5.0		6,500.00		5.0		6,500.00	
Rent	1,000.00	-30.0	-300.00	700.00		+30.0	+300.00	1,300.00	
Maintenance/repair	202.85	-30.0	-60.86	142.00		+30.0	+60.86	263.71	
Total	**384,105.27**			**303,361.49**	-21.02%			**464,368.14**	+20.89%

BRL 37.12 (USD 11.67). Considering the best scenario, with 15 participants per group session, the per capita cost was reduced by approximately 33%, i.e. the group session with an occupational therapist with 10 participants had a per capita cost of BRL 3.74 and, with 15 participants, the value dropped to BRL 2.50. In the worst scenario, in which there were only five participants per group session, the per capita cost was raised by approximately 100%, i.e. the per capita cost of the group session with a social worker rose to BRL 7.93, and with a psychologist to BRL 5.62. Overall, in the worst scenario, the IPC would be 20.4% more expensive, and in the best scenario, 6.7% cheaper.

DISCUSSION

The Brazilian federal government spent BRL 39,780.00 per CAPS-ad in 2015,[12] and the present study showed that the mean monthly cost of this service was BRL 64,017.54 in the same year, i.e. federal funding covered 62.1% of the total costs of the CAPS-ad examined here. This CAPS-ad offered treatment for an average of 135 patients per month and, according to the federal-to-municipal government funding ratio, the federal government invested BRL 294.47 (USD 92.60, using PPP) and the municipal government BRL 179.73 (USD 56.51, using PPP) for each patient assisted. To use this resource as effectively as possible, it is necessary to ascertain strict eligibility criteria for treatment proposals, especially when considering the huge difference in costs between the packages of care.

Healthcare staff accounted for 56.5% of the total CAPS-ad cost. This result was close to the findings of Araujo et al.,[13] who showed that the expenditure on human resource payments represented 75.9% of all Brazilian municipal governments' expenditure, regarding all healthcare expenses. Moreover, another cost analysis study by Razzouk et al.,[14] on residential facilities in the city of São Paulo, showed that human resources accounted for 61.4% of its total costs. Even though the CAPS-ad of the present study may not be representative of all Brazilian CAPS-ad in some respects, its total estimated costs may be considered comparable to those of other CAPS-ad given that it followed the standard regulations regarding healthcare staff composition,[15] which represents the greatest part of the costs.

The Rio Claro municipal government funded 37.9% of the monthly CAPS-ad costs, or BRL 64,017.54. In that same year, the total budget of the city council was BRL 698 million, and 30% (BRL 209 million) was invested in healthcare according to the official city council newspaper.[15] Thus, 0.36% of the total municipal healthcare budget was invested in the only specialized service for psychosocial rehabilitation that assisted drug users in the city.

Although the federal government's budget covered a large part of the CAPS-ad costs, there have been no adjustments for inflation since 2011,[12] regarding the resources allocated to municipal governments for financing CAPS-ad, which may have made these resources less significant over time. Therefore, given that the resource allocation from the federal to the municipal government for funding specific services is insufficient, municipal managers have become obliged to increase their contribution towards maintenance of these services.[13] Thus, municipalities have become the Brazilian governmental level that contributes most to the healthcare sector in proportional terms, i.e. in relation to its tax collection.[16,17]

The monthly CAPS-ad treatment cost per capita was almost three times lower than the amount paid per month (BRL 1,350.00) by the São Paulo state government to provide inpatient treatment for substance users at private clinics through the "restart program" (Programa Recomeço).[18] It is important to underscore that the decision-making process regarding public resource allocation between different services should be based not only on costs but also on patients' needs and profiles. Moreover, the differences in

Table 5. One-month package-of-care costs per capita in Brazilian reais (BRL)

Mental health treatment	IPC		SIPC		NIPC	
	Quantity	Total cost	Quantity	Total cost	Quantity	Total cost
Visit to psychiatrist	1	28.16	1	28.16	1	28.16
Visit to general practitioner	1	28.16	1	28.16	0	0
Group session with occupational therapist	12	44.88	8	29.92	0	0
Group session with social worker	10	39.60	4	15.84	0	0
Group session with psychologist	12	33.60	8	22.40	0	0
Group session with nurse	6	17.82	4	11.88	0	0
Individual session with assistant nurse	20	67.00	12	40.20	0	0
Individual session with health case manager	8	179.92	4	89.96	0	0
Group session with health case manager	–	–	–	–	4	8.96
Lunch	20	220.00	12	132.00	0	0
Snacks	40	9.20	24	5.52	0	0
Total cost per month		**668.34**		**404.04**		**37.12**

IPC = intensive package of care; SIPC = semi-intensive package of care; NIPC = non-intensive package of care.

costs mentioned above were not compared with differences in outcomes or according to sample characteristics. However, it is also important to establish strict criteria for using more expensive services, in accordance with patients' needs, in order to optimize the public resource allocation.

The unit costs reported here may inform further economic evaluations and modelling studies within similar contexts of services in the state of São Paulo. This is especially important, considering the lack of information on unit costs within healthcare in Brazil. This is unlike the situation in some European countries, where national guidelines for unit costs reference for healthcare services and interventions are available, thus facilitating development of cost studies and economic evaluations.[19,20] There is a lack of cost-effectiveness studies in Brazil, especially in relation to mental health, and the findings from the present study may be useful for further studies in this regard.

The expansion of the CAPS network in Brazil[1] and the way in which public resource allocation for funding a CAPS-ad occurs[8,15] show that only at the federal level is there any specific budget for this purpose. A specific budget for mental health actions has been placed as a priority for mental health policies worldwide,[21-22] and Brazilian states and municipalities need to ensure transparency in the way that they apply resources for mental health services.

According to the current legislation on public health financing in Brazil,[23,24] municipalities and states should, respectively, allocate minimums of 15% and 12% of their budgets to public health. However, state governments' participation in the cost of CAPS in Brazil remains a challenge and has been the subject of interpellation instigated by municipalities, with the aim of achieving greater participation from state governments, so as to ensure sustainability of these services.[1]

It is necessary to ascertain municipal governments' capacity to manage the costs of these services, in order to plan public investment in services that can be sustained over time. After the costs of this type of service have been established, the discussion can shift from focusing on coverage to analysis in greater depth, including in relation to the cost-effectiveness of services and interventions.

The present study has three important limitations:

1. the state government may have participated in the purchase of medications prescribed by CAPS-ad doctors, and thus its participation in the CAPS-ad funding system may have been underestimated;
2. the study period may not have detected possible fluctuations in costs over the twelve months of the year; and
3. there is some uncertainty regarding inaccuracies of cost estimations, given the variations in healthcare staff salaries, revenue and medication costs according to the different regions of Brazil. These limitations impede generalizations.

CONCLUSIONS

The federal government funded two-thirds of the CAPS-ad costs, while one-third was funded by the municipal government. These findings may enable better planning and management, both for the federal government and for municipal governments that are interested in expanding the CMHS network for people with substance-related disorders. Moreover, these findings also highlight the need for government agencies and the national academic community to focus on mental health policies, not only to expand treatment coverage, but also to attain the best allocation of resources, in terms of costs and outcomes. Careful use of packages of care based on patient needs can improve people's mental health and avoid wasting resources.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. DAPES. Coordenação Geral de Saúde Mental, Álcool e Outras Drogas. Saúde Mental no SUS : cuidado em liberdade, defesa de direitos e Rede de Atenção Psicossocial. Relatório de Gestão 2011-2015. Brasília: Ministério da Saúde; 2016.
2. Gazal-Carvalho C, Carlini-Cotrim B, Silva OA, Sauaia N. Prevalência de alcoolemia em vítimas de causas externas admitidas em centro urbano de atenção ao trauma [Blood alcohol content prevalence among trauma patients seen at a level 1 trauma center]. Rev Saude Publica. 2002;36(1):47-54. PMID: 11887229; doi: 10.1590/S0034-89102002000100008.
3. Moraes E, Laranjeira R. Custo Social do "beber e dirigir" na Cidade de São Paulo [thesis]. São Paulo: Universidade Federal de São Paulo; 2013. Available from http://www.bv.fapesp.br/pt/bolsas/41786/custo-social-do-beber-e-dirigir-na-cidade-de-sao-paulo/. Accessed in 2018 (Jul 3).
4. Fonseca AM, Galduróz JC, Tondowski CS, Noto AR. Padrões de violência domiciliar associada ao uso de álcool no Brasil [Alcohol-related domestic violence: a household survey in Brazil]. Rev Saúde Pública. 2009;43(5):743-9. PMID: 19722004; doi: 10.1590/S0034-89102009005000049.
5. Beecham J, Knapp M. Costing Psychiatric Interventions. In: Thornicroft G, Brewin C, Wing J, editors. Measuring Mental Health Needs. 2nd ed. London: RCPsych Publications; 2001. p. 200-224. isbn: 9781901242607.
6. Benegal V, Chand PK, Obot IS. Packages of care for alcohol use disorders in low- and middle-income countries. PLoS Med. 2009;6(10):e1000170. PMID: 19859536; doi: 10.1371/journal.pmed.1000170.
7. Drummond M, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. United Kingdom: Oxford University Press; 2015. p. 445. isbn: 9780191643583.
8. Brasil. Ministério da Saúde. Secretaria-Executiva. Coordenação de Apoio à Gestão Descentralizada. Diretrizes operacionais para os pactos pela vida, em defesa do SUS e de gestão/Ministério da Saúde, Secretaria-Executiva, Coordenação de Apoio à Gestão Descentralizada. u2013 Brasília: Editora do Ministério da Saúde, 2006. ISBN: 85-334-0960-5.

9. Anuário do Sistema Público de Emprego, Trabalho e Renda 2016: Remuneração: livro 6/Departamento Intersindical de Estatística e Estudos Socioeconômicos. São Paulo: DIEESE; 2017. Available from: https://www.dieese.org.br/anuario/2017/Livro6_Remuneracao.html. Accessed in 2018 (Jul 3).
10. Fundação Instituto de Pesquisas Econômicas - FIPE. Índice Fipezap de Preços de Imóveis Anunciados; 2015. Available from: http://www.fipe.org.br/pt-br/indices/fipezap/. Accessed in 2018 (Jul 3).
11. Organization for Economic Co-operation and Development- OECD/Eurostat. Eurostat-OECD Methodological Manual on Purchasing Power Parities (2012 Edition). Paris: OECD Publishing; 2012. Available from: https://doi.org/10.1787/9789264189232-en. Accessed in 2018 (Aug 31).
12. Brasil, Ministerio da Saúde. Portaria no 3.089, de 23 de dezembro de 2011 (republicada) – Dispõe, no âmbito da Rede de Atenção Psicossocial, sobre o financiamento dos Centros de Atenção Psicossocial (CAPS). Brasília: Ministério da Saúde; 2011. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2011/prt3089_23_12_2011_rep.html. Accessed in 2018 (Jul 3).
13. Araújo CE, Gonçalves GQ, Machado JA. Os municípios brasileiros e os gastos próprios com saúde: algumas associações [Brazilian municipalities and their own expenditures on health: some associations]. Cien Saude Colet. 2017;22(3):953-63. PMID: 28301002; doi: 10.1590/1413-81232017223.15542016.
14. Razzouk D. Estimating costs of residential facilities. In: Razzouk D, editor. Mental Health Economics. The Costs and Benefits of Psychiatric Care. 1st ed. São Paulo: Springer International Publishing; 2017. p. 253-266. ISBN: 978-3-319-55265-1.
15. Imprensa da Prefeitura de Rio Claro. Orçamento municipal de Rio Claro para 2015 é de R$ 698 milhões. Imprensa da Prefeitura Municipal de Rio Claro – SP [Internet]. 2015 [cited 2017 Aug 11]. p. 1. Available from: http://imprensa.rioclaro.sp.gov.br/?p=25503. Accessed in 2018 (Jul 3).
16. Faveret ACSC. A vinculação constitucional de recursos para a saúde : avanços, entraves e perspectivas. Ciênc Saúde Coletiva. 2003;8(2):371-8. doi: 10.1590/S1413-81232003000200004.
17. Santo AC, Tanaka OY. Financiamento, gasto e oferta de serviços de saúde em grandes centros urbanos do estado de São Paulo (Brasil) [Health care financing, expenditure and supply in great urban centers in the state of São Paulo (Brazil)]. Cien Saude Colet. 2011;16(3):1875-85. PMID: 21519676; doi: 10.1590/S1413-81232011000300022.
18. Assembleia Legislativa do Estado de São Paulo. Decreto no 61.674, de 02 de dezembro de 2015 - Reorganiza o "Programa Estadual de Enfrentamento ao Crack - Programa Recomeço", que passa a denominar-se "Programa Estadual de Políticas sobre Drogas - Programa Recomeço: uma vida sem drogas". São Paulo; 2015. Available from: http://www.al.sp.gov.br/repositorio/legislacao/decreto/2015/decreto-61674-02.12.2015.html. Accessed in 2018 (Jul 3).
19. Curtis L, Burns A. Unit Costs of Health & Social Care 2016. Personal Social Services Research Unit. Canterbury: University of Kent; 2016. ISBN: 978-1-911353-02-7.
20. McCrone P, Thornicroft G, Phelan M, et al. Utilization and costs of community mental health services. PRiSM Psychosis Study 5. Br J Psychiatry. 1998;173:391-8. PMID: 9926055; doi: 10.1192/bjp.173.5.391.
21. Lancet Global Mental Health Group, Chisholm D, Flisher A, et al. Scale up services for mental disorders: a call for action. Lancet. 2007;370(9594):1241-52. PMID: 17804059; doi: 10.1016/S0140-6736(07)61242-2.
22. Eaton J, McCay L, Semrau M, et al. Scale up of services for mental health in low-income and middle-income countries. Lancet. 2011;378(9802):1592-603. PMID: 22008429; doi: 10.1016/S0140-6736(11)60891-X.
23. Núcleo de Saúde da Consultoria de Orçamento e Fiscalização Financeira da Câmara dos Deputados. Financiamento da saúde : Brasil e outros países com cobertura universal. A participação estatal no financiamento de sistemas de saúde e a situação do Sistema Único de Saúde - SUS. Brasilia: Câmara dos Deputados, Consultoria de Orçamento e Fiscalização Financeira; 2013. Available from: http://bd.camara.gov.br/bd/handle/bdcamara/21159#. Accessed in 2018 (Jul 3).
24. Ministério da Saúde. Lei Complementar nº 141 de 13 de Janeiro de 2012 - Regulamenta o § 3º do art. 198 da Constituição Federal para dispor sobre os valores mínimos a serem aplicados anualmente pela União, Estados, Distrito Federal e Municípios em ações e serviços públicos de saúde; estabelece os critérios de rateio dos recursos de transferências para a saúde e as normas de fiscalização, avaliação e controle das despesas com saúde nas 3 (três) esferas de governo; revoga dispositivos das Leis nos 8.080, de 19 de setembro de 1990, e 8.689, de 27 de julho de 1993; e dá outras providências. Brasília: Ministério da Saúde; 2012. Available from: http://conselho.saude.gov.br/legislacao/index.htm. Accessed in 2018 (Jul 3).

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Supplementary File.

Table S1. Description and estimation of CAPS-ad equipment costs according to website consultation in September 2015

Equipment	Quantity	Brand and model	Year of purchase	Websites consulted	Cost per unit (R$)
Desktop computer	4	Lenovo V520s, Intel Core I3, 2 GB, 500 GB	2012	americanas.com.br magazineluiza.com.br submarino.com.br	800.00
Computer monitor	4	LG Monitor 20M37AA	2012	americanas.com.br magazineluiza.com.br walmart.com.br	340.00
Printer	1	HP Deskjet Multifunction (p2035)	Before 2010	americanas.com.br magazineluiza.com.br walmart.com.br	499.00
Refrigerator	1	Refrigerator with one door, Consul	Before 2010	casasbahia.com.br magazineluiza.com.br extra.com.br	870.00
Stove	1	Four-burner stove, Consul	Before 2010	casasbahia.com.br magazineluiza.com.br extra.com.br	570.00

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Development and validation of a whole-cell ELISA for serologically diagnosing *Helicobacter pylori* infection in Brazilian children and adults: a diagnostic accuracy study

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KEY WORDS:
Helicobacter pylori.
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Child.
Adult.

ABSTRACT

BACKGROUND: Serological tests are practical, with low cost, but no noninvasive tests are available for diagnosing *Helicobacter pylori* (*H. pylori*) infection in Brazil. The aim here was to develop and validate enzyme-linked immunosorbent assay (ELISA) serological tests to detect anti-*H. pylori* immunoglobulin G antibodies, based on cultured strains from Brazilian patients.

DESIGN AND SETTING: Cross-sectional, diagnostic accuracy study comparing a locally developed and validated ELISA and invasive tests among dyspeptic patients at two public hospitals in São Paulo, Brazil.

METHODS: An ELISA test was prepared using whole-cell antigen from 56 strains. After genotypic characterization, it was standardized and optical density (OD) cutoffs were determined based on the serum antibody response of 100 *H. pylori*-negative samples, compared with 82 *H. pylori*-positive samples. Validation was performed on 174 symptomatic patients.

RESULTS: The optimal OD cutoffs established (for monoclonal and polyclonal tests, respectively) were 0.167 and 0.164; overall ELISA sensitivity: 84.3%, 78.9%; specificity: 88.6%, 90.6%; positive predictive value (PPV): 75.4%, 80%; negative predictive value (NPV): 93.1%, 81.8%; accuracy: 87.3%, 86.2%; child and adolescent ELISA sensitivity: 74.2%, 81.8%; specificity: 90.8%, 86.7%; PPV: 66.6%, 84.3%; NPV: 95.8%, 84.8%; accuracy: 88.5%, 84.6; adult ELISA sensitivity: 84.4%, 75%; specificity: 86.9%, 93%; PPV: 81.8%, 78.3%; NPV: 88.9%, 91.8%; accuracy: 85.9%, 88.5%.

CONCLUSION: The polyclonal serological test developed using local strains presented better diagnostic performance among children and adolescents, while the monoclonal test was better among adults. The results from both tests suggest that these in-house serological tests could be used to detect anti-*H. pylori* antibodies in our population, for screening purposes.

INTRODUCTION

Helicobacter pylori (*H. pylori*) colonizes the stomach of more than half of the world's population, mainly in developing countries.[1,2] In fact, the burden of *H. pylori* infection is mostly borne by developing countries and specific high-risk groups in poor communities.[3]

This infection is associated with chronic gastritis, peptic ulcer disease and mucosa-associated lymphoid tissue (MALT) lymphoma in children and adults, and with development of gastric cancer, which occurs typically in adulthood.[4] Although the incidence and mortality rates for gastric cancer have been slowly decreasing in many countries over the last five decades, it is still the fifth most common cause of cancer-related deaths, and more than 70% of gastric cancer cases occur in developing countries.[5] Thus, gastric cancer will still remain an important healthcare problem over the coming decades, particularly in poor communities.

Recently, we demonstrated that *H. pylori* eradication plays a role in the treatment of chronic immune thrombocytopenic purpura (ITP) in children.[6] Moreover, a systematic review study has shown that, among adults, detection and eradication of *H. pylori* infection should be considered in the management of patients with seemingly typical ITP.[7]

Different diagnostic methods are used to assess *H. pylori* infection. To perform the rapid urease test, culturing, polymerase chain reaction (PCR) and histological analysis, the invasive procedures of esophagogastroduodenoscopy and gastric biopsy are required. Among the methods that are usually considered "noninvasive" for *Helicobacter* infection (serological tests, C^{13}-urea

breath test and stool antigen test), detection of serum-specific anti-*H. pylori* antibodies is the only one available in Brazil, and this is limited to a few laboratories in big cities.

Anti-*H. pylori* immunoglobulin G (IgG) antibody detection by means of the enzyme-linked immunosorbent assay (ELISA) is the third-best method for noninvasive screening for *H. pylori* infection.[8] It might be suggested as the first method, in high-prevalence areas, if the urea breath test and stool antigen test are not available.[9] Furthermore, serological tests are considered to be the most efficient diagnostic method under certain clinical situations in which local changes in the stomach may affect the results from other tests (i.e. in cases of gastrointestinal bleeding, atrophic gastritis, gastric MALT lymphoma and gastric carcinoma), or when antibiotics or proton pump inhibitors are used.[8] ELISA tests developed using *H. pylori* antigens from local samples usually present better accuracy than that of commercial tests based on non-local *H. pylori* antigen. One of the main criticisms of commercial tests is that they are widely used in any population (including in developing countries). Therefore, development of a local test has been encouraged.[10-17] Hence, an easily performed, low-cost, locally developed and validated noninvasive test, for widespread use, might be recommendable for screening for *H. pylori* infection. In particular, use of such tests might potentially reduce the need to perform invasive tests, in a test-and-treat strategy.

OBJECTIVE

The aims of this study were to develop and validate an ELISA-based serological test using whole-cell antigen of cultured *H. pylori* from gastric biopsies on Brazilian patients, in order to detect anti-*H. pylori* IgG antibodies in children and adults.

METHODS

Design and setting

This was a cross-sectional diagnostic accuracy study, in which a serological test to diagnose *Helicobacter pylori* infection was developed. The locally developed ELISA serological test was standardized and the optical density (OD) cutoff was determined based on the serum antibody responses of 100 *H. pylori*-negative uninfected patients. A cross-sectional study comparing this in-house ELISA serological test with invasive tests was conducted among 174 consecutive dyspeptic patients at two public hospitals in São Paulo, Brazil.

Gastric biopsy samples and strain isolation

We examined a series of preserved frozen cultures (-80 °C) that had been isolated from gastric biopsy samples from 29 children and adolescents and 27 adult patients who were attended at the endoscopy units of two public hospitals: Hospital São Paulo, a university hospital, and Hospital Infantil Cândido Fontoura, a secondary-level children's hospital, which are both in the city of São Paulo, Brazil. Antral gastric biopsies were processed and cultured in brain-heart infusion (BHI) agar (BHI Agar, BD Difco, Becton-Dickinson, NJ, USA), on plates that were incubated for 10-14 days under microaerophilic conditions, as previously described.[18]

Virulence gene detection by means of conventional PCR

Samples of bacteria were harvested from a three-day-old culture and were suspended in 1 ml of distilled water for deoxyribonucleic acid (DNA) extraction (Wizard genomic DNA purification kit, Promega), in accordance with the manufacturer's instructions. For *H. pylori* DNA confirmation, a PCR specific for the *H. pylori* UreA and B genes was used.[19] PCR amplification of the VacA signal sequence and midregion, and of the gene CagA, was performed as previously described.[20,21] Negative and positive controls were included in all reactions.

The gene CagA was identified in 27/56 (48.2%). The gene VacA s1 was observed in 41/56 (73.2%) and VacA s2 in 15/56 (26.8%). The allele VacA m1 was identified in 35/56 (60.7%) and m2 in 21/56 (39.3%): s1m1 occurred in 31/56 (55.3%), s1m2 in 10/56 (17.8%), s2m1 in 3/56 (5.3%) and s2m2 in 12/56 (21.4%).

Antigen preparation

Whole-cell antigen from a sonicated pool (Ultrasonic Disruptor QR500W, Ultronique, Brazil) of 56 strains was obtained as previously described.[22] Antigen preparation was adjusted to a protein concentration of 1 mg/ml,[23] and aliquots of 100 µl were stored at -20 °C until used.

ELISA standardization

Detection of anti-*H. pylori* IgG antibodies was, firstly, tested on 10 *H. pylori*-positive patients (five adults and five children) and 10 *H. pylori*-negative patients (five adults and five children), who formed positive and negative serum controls, respectively. Their diagnoses were based on invasive methods: the gold standard for positive diagnoses was a positive culture and/or positive histological test and a positive rapid urease test; and, for negative diagnoses, all three tests needed to be negative.

Standardization was performed as previously described by Camorlinga-Ponce et al.[23] For each assay, the optimal antigen concentration and working serum dilution were determined based on checkerboard titrations. ELISA plates were prepared as previously described.[22]

Polyclonal and monoclonal antibodies were used to evaluate the best detection test. Polyclonal antibodies comprise collections of antibodies from different B cells that recognize multiple epitopes on the same antigen. For this reason, they provide greater sensitivity,

even for detecting proteins that are present in low quantities in a sample. In contrast, monoclonal antibodies comprise antibodies from a single antibody-producing B cell. Thus, they bind with a single epitope. This is highly specific, with only a small risk of cross-reactivity, and it can provide better results in assays requiring quantification of the protein levels.

For the polyclonal test (peroxidase-conjugated polyclonal anti-human IgG antibodies; Sigma), color was developed using 100 µl of 0.4 mg/ml ortho-phenylenediamine dihydrochloride diluted in citrate-phosphate buffer and 0.03% sodium perborate (Sigma) as the substrate. The plates were incubated under dark conditions at 37 °C and, after 20 minutes, 50 µl of stop solution (2M H_2SO_4) was added to each well. Absorbance was read at 492 nm (Multiskan FC microplate photometer). For the monoclonal test (alkaline phosphatase-conjugated monoclonal anti-human IgG antibodies; Sigma), color was developed using 100 µl of 1 mg/ml p-nitrophenylphosphate (Sigma) and absorbance was read at 405 nm (Multiskan FC microplate photometer). All reactions were performed in triplicate, and the mean of three optical density (OD) measurements was used.

Analysis on the checkerboard titration for polyclonal antibodies showed that the following were the optimal concentrations: for antigen preparation, 1:500 (2 µg/ml); for working serum dilution, 1:400; and for peroxidase-conjugated anti-human antibodies, 1:60,000. For monoclonal antibodies, the following were the optimal concentrations: for antigen preparation, 1:300 (3.3 µg/ml); for working serum dilution, 1:400; and for alkaline phosphatase-conjugated anti-human antibodies, 1:25,000. The best reading time for monoclonal antibodies was 25 minutes. ELISA tests were run for four consecutive days to evaluate interoperability and reproducibility.

Antigen specificity

The cross-reactivity of the in-house ELISA serological tests for *H. pylori* antigens was evaluated against whole-cell antigens or membrane proteins of 14 heterologous bacterial species: *Campylobacter jejuni*, *Escherichia coli*, *Pseudomonas aeruginosa* (mucoid), *Pseudomonas aeruginosa* (nonmucoid), *Burkholderia cepacia*, *Klebsiella pneumoniae, Klebsiella sp., Proteus mirabilis, Proteus vulgaris, Shigella flexneri, Shigella sp., Salmonella typhi, Salmonella enterica* and *Salmonella sp*. These reactions were performed through competitive inhibition assays, as previously described.[24] No positive reactions were observed.

Determination of cutoff

The optical density (OD) cutoffs for the monoclonal and polyclonal tests were determined based on the serum antibody responses of 100 samples (50 adults and 50 children and adolescents) from *H. pylori*-negative uninfected patients, based on the gold standard. Thus, a pool of these 100 serum samples was used as the negative serum control. The threshold for positivity was defined as the mean value plus three standard deviations of the optical density, as previously described.[23]

These values were compared with the values from a collection of 82 serum samples (33 adults and 49 children and adolescents) from *H. pylori*-positive infected patients, based on the gold standard, which presented OD values above the corresponding cutoff, without showing any overlapping values. A pool of these 82 samples was used as the positive serum control.

During the testing of the unknown samples, a positive serum pool was included in quadruplicate in every plate and the mean of the four OD values was used to calculate the threshold for that plate. The results from each serum sample were defined as the ratio of the OD value of the sample to the threshold value and were expressed in ELISA units (EU). Serum samples with EU > 1.0 were considered seropositive.

Validation of in-house ELISA serological assay

Peripheral blood samples (10 ml) were collected by means of venous puncture from 174 patients on whom esophagogastroduodenoscopy had been performed. The serum was stored at -20 °C. The following were taken to be exclusion criteria: recent use of antibiotics, H2 receptor antagonists, proton pump inhibitors and/or bismuth salts, and presence of digestive or extradigestive chronic diseases. Six gastric biopsies were taken for the rapid urease test and for histological evaluation (one from the gastric body and one from the antrum, for each of these), and for culturing (two from the antrum). The procedures were performed as previously described.[18,25]

Statistical analysis

Qualitative variables were described in terms of their proportions, and quantitative variables were described in terms of their means and standard deviations. Analyses on continuous variables were based on the negative gold standard (negative rapid urease test, histological evaluation and culturing). The threshold for positivity was defined as the mean value plus three standard deviations of the optical density. The positive serum control was standardized using the positive gold standard (positive culture and/or positive histological evaluation and rapid urease test) and presence of a positive serological test, i.e. OD over the established cutoff value. The OD for each serum sample was determined in triplicate. The optimal OD cutoff was determined based on receiver operating characteristic (ROC) curves using different sensitivity and specificity values, and the area under the ROC curve (AUC) was estimated taking the significance level to be an accuracy value of 0.5.

The sample size calculation for in-house ELISA serological test validation was based on a prevalence of *H. pylori* infection of

around 30% in children and 50% in adults in Brazil. The desirable AUC was considered to be 0.90, with a significance level of 0.05 and absolute precision of 5%. Thus, for this study, the sample size was estimated to be 78 adults and 95 children.

The sensitivity, specificity, accuracy and positive and negative predictive values of the in-house ELISA serological tests were evaluated by comparing OD values, based on cutoffs that were determined using the ROC curve, against the gold standard (rapid urease test, histological evaluation and culturing). Negative and positive likelihood ratios were evaluated.

Ethical considerations

This study was approved by the Institutional Review Board of the Federal University of São Paulo (Universidade Federal de São Paulo), under registration number 180.606, on December 21, 2012, and under Brazil Platform registration number (CAAE) 10235612.0.0000.5505. All patients and/or their guardians were informed about the purposes of this study and signed an informed consent form.

RESULTS

Patients

Between November 2015 and August 2017 (20 months), 847 children and adolescents and 432 adults were evaluated by means of esophagogastroduodenoscopy at Hospital São Paulo, a university hospital, and Hospital Infantil Cândido Fontoura, a secondary-level children's hospital, which are both in the city of São Paulo, Brazil. *H. pylori* status was defined by means of the gold standard described here, and, for validation purposes, no equivocal findings were included. To validate our in-house serological test, 174 consecutive dyspeptic patients, for whom the *H. Pylori* infection status was unknown were chosen: 96 children and adolescents (age range 2-17 years; mean: 12.2 ± 3.7 years) and 78 adult (age range 19-85 years; mean: 52.3 ± 18.1 years). The esophagogastroduodenoscopy findings were normal in 108/174 patients (62%) and abnormal in 66/174 (38%). Among the latter, 57/174 (32.7%) were *H. pylori*-positive. Among the children and adolescents of this sample, 24/96 (25%) were *H. pylori*-positive; while among the adults, 33/78 (42.3%) were *H. pylori*-positive.

Determination of cutoff

The serum samples that were negative in the monoclonal test presented OD values ranging from 0.085 to 0.155 (mean ± standard deviation, SD: 0.11996 ± 0.017695). The threshold for positivity was 0.173. The serum samples that were negative in the polyclonal test presented OD values ranging from 0.061 to 0.148 (mean ± SD: 0.10336 ± 0.0164024). The threshold for positivity was 0.153. The serum samples (82 samples) that were positive in the monoclonal test presented OD values ranging from 0.180 (1.04 EU) to 0.464 (2.85 EU) (mean ± SD: 0.22968 (1.33 EU) ± 0.057). The serum samples (82 samples) that were positive in the polyclonal test presented OD values ranging from 0.172 (1.12 EU) to 0.437 (2.85 EU) (mean ± SD: 0.261 (1.7 EU) ± 0.06019).

Despite the threshold for positivity based on the mean for the negative results plus 3 SD in the monoclonal test (0.173) and in the polyclonal test (0.153), the optimal OD cutoff value based on ROC curve analysis was found to be 0.167 in the monoclonal test, with an area under the ROC curve of 0.9 (95% confidence interval, CI: 0.87-0.92). The optimal OD cutoff value was 0.164 in the polyclonal test, with an area under the ROC curve of 0.915 (95% CI: 0.89-0.93).

Validation of the ELISA serological assay

Analysis on the overall seropositive results (EU > 1.0) from the monoclonal test presented little difference in values, compared with the polyclonal test, but the sensitivity and negative predictive values were slightly higher with monoclonal antibodies. When age was considered, the monoclonal test presented a better result for sensitivity among adults, but specificity was better among children and adolescents. In contrast, the polyclonal test presented a better result for sensitivity among children and adolescents. The accuracy was slightly better among children and adolescents in the monoclonal test and among adults in the polyclonal test (**Table 1**).

DISCUSSION

In this study, ELISA-based serological tests to detect monoclonal and polyclonal IgG antibodies using *H. pylori* whole-cell antigen from strains isolated in our community were developed, standardized, validated and evaluated. The sensitivity and specificity of the in-house serological tests for both polyclonal antibodies (78.9% and 90.6%) and monoclonal antibodies (84.3% and 88.6%) were similar to those found by Camorlinga-Ponce et al.[23] (85% and 89.7%). The in-house ELISA serological test that we developed did not present any cross-reactivity to heterologous bacterial species.

The sample size was appropriate, given that both the sensitivity and the specificity presented narrow 95% confidence intervals. Selectivity in relation to gastroduodenal diseases can influence the sensitivity and specificity results. A study conducted by Aziz et al.[17] found higher OD values and this may have occurred because their study was based on peptic ulcer disease patients. In the present study, adults, children and adolescents were evaluated together, and the OD results presented little variation. However, other studies conducted on Brazilian populations have shown that age had an influence on the sensitivity and specificity of commercial tests.[26-27]

Both commercial and in-house serological tests have presented large ranges of sensitivity and specificity results. Leal et al.[14] conducted a meta-analysis that including 42 studies in which ELISA serological tests were performed on samples from children to detect *H. pylori* infection. There were 33 studies using 19 different commercial tests and nine studies using in-house tests. They observed that the mean sensitivity was 79.2% (95% CI: 77.3-81%) and that the mean specificity was 92.4% (95% CI: 91.6-93.3%). On the other hand, an in-house serological test that was developed in Pakistan presented sensitivity of 92% and specificity of 100%, i.e. similar to or better than commercial tests.[17]

The accuracy of serological tests can also be affected by the choice of antigen that is used to prepare the in-house ELISA assay. In some studies, *H. pylori* genetic heterogeneity was taken into consideration in choosing the whole-cell lysate (with sonication).[28,29] In our study, the strains used in the antigenic pool were verified genetically, to obtain better representativeness, including the CagA and VacA strains (alleles s1m1, s1m2, s2m1 and s2m2). The genotypic distribution in our study was similar to what has been found in other studies in Brazil.[30,31]

The diagnostic accuracy of a serological test is enhanced when the antigen pool is prepared based on multiple strains. Widmer et al.[32] evaluated the performance of three antigenic preparations and observed that the results were superior when an enzyme immunoassay prepared with a pool of native antigens was used (sensitivity: 90-100%; specificity: 90-97%), rather than with recombinant antigen (sensitivity: 59-78%; specificity: 41-100%). Serological tests based on whole-cell antigen or whole-cell antigen lysate have also shown good performance among both children and adult patients.[11,23,24,33]

Despite the simplicity of ELISA serological tests, attention during their development is needed. In particular, the optimal antigen concentration, serum sample dilution and antibody conjugation need to be determined. These parameters should be optimized and adjusted to local conditions, to the population studied and to the method developed.[17,34] The optimal concentrations in the present study were determined by means of the checkerboard titration method. It is very important to make these determinations because of false-positive titration results caused by high concentrations of antigens, which promote nonspecific bonds, even in negative serum. Moreover, low antigen concentrations can result in false negatives. In addition, high concentrations of conjugated antibodies may result in nonspecific reading, while low concentrations cause decreased OD. The serum concentration can also interfere with the OD results.[17]

This study was the first on our population to evaluate the serological response to anti-*H. pylori* IgG antibodies among symptomatic children, adolescents and adult patients, using an ELISA-based serological test developed using whole-cell antigen lysate from strains collected in our own community.

Ideal tests for screening purposes should present high sensitivity and good specificity. The serological test using monoclonal antibodies that was developed in this study presented sensitivity of over 80% among adults, while the serological test using polyclonal antibodies presented sensitivity of over 80% among children and adolescents. This indicates that these tests are suitable for population-based screening, especially the polyclonal test, which is characterized by greater sensitivity. On the other hand, although the higher specificity among adults in the polyclonal test, with low

Table 1. Analysis on serological tests (sensitivity, specificity, accuracy, positive and negative predictive values and positive and negative likelihood ratios)

Type of test	Category	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)	Positive likelihood ratio	Negative likelihood ratio
Monoclonal	General	84.3 (83.4-85.3)	88.6 (85.9-87.9)	75.4 (74.5-76.3)	93.1 (92-94.1)	87.3 (86.3-88.3)	7.4	0.18
	Children and adolescents	74.2 (82.5-85.9)	90.8 (88.9-92.7)	66.6 (65.2-67.9)	95.8 (93.8-97.7)	88.5 (86.7-90)	8	0.28
	Adults	84.4 (82.3-86.5)	86.9 (84.7-89)	81.8 (79.7-83.9)	88.9 (86.7-91.1)	85.9 (83.7-88)	6.4	0.18
Polyclonal	General	78.9 (75.8-82)	90.6 (88.4-92.8)	80 (77-83)	81.8 (78.9-84.7)	86.2 (83.6-88.8)	8.4	0.23
	Children and adolescents	81.8 (77.4-86.2)	86.7 (82.8-90.5)	84.3 (80.2-88.4)	84.8 (80.7-88.8)	84.6 (80.5-88.7)	6.1	0.21
	Adults	75 (70.6-79.4)	93 (90.4-95.6)	78.3 (74.1-82.5)	91.8 (89-94.6)	88.5 (85.2-91.7)	10.7	0.27

PPV = positive predictive value; NPV = negative predictive value.

occurrence of false-negative results, is desirable for a diagnostic method, it is not necessary for a screening test.

CONCLUSION

The in-house polyclonal serological test that was developed using local strains (in-house) presented better diagnostic performance than did the monoclonal test for children and adolescents. In contrast, the monoclonal test was better among adults. The results relating to accuracy, sensitivity, specificity and likelihood ratios from both tests suggest that these in-house serological tests could be used to detect anti-*H. pylori* antibodies in the Brazilian population, for screening purposes.

REFERENCES

1. Go MF. Review article: natural history and epidemiology of *Helicobacter pylori* infection. Aliment Pharmacol Ther. 2002;16(Suppl 1):3-15. PMID: 11849122.
2. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of *Helicobacter pylori* infection. Helicobacter. 2014;19(Suppl 1):1-5. PMID: 25167938; doi: 10.1111/hel.12165.
3. Roque JRDS, Machado RS, Rodrigues D, Rech P, Kawakami E. Prevalência de infecção por *Helicobacter pylori* em uma comunidade indígena em São Paulo e fatores associados: estudo transversal [Prevalence of *Helicobacter pylori* infection in an indigenous community in São Paulo and associated factors: cross-sectional study]. São Paulo Med J. 2017;135(2):140-5. doi: 10.1590/1516-3180.2016.0114091216.
4. Correa P, Piazuelo MB. *Helicobacter pylori* infection and gastric adenocarcinoma. US Gastroenterol Hepatol Rev. 2011;7(1):59-64. PMID: 21857882.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. PMID: 25220842; doi: 10.1002/ijc.29210.
6. Brito HSH, Braga JA, Loggetto SR, et al. *Helicobacter pylori* infection and immune thrombocytopenic purpura in children and adolescents: A randomized controlled trial. Platelets. 2015;26(4):336-41. PMID: 2483281; doi: 10.3109/09537104.2014.911836.
7. Stasi R, Sarpatwari A, Segal JB, et al. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. Blood. 2009;113(6):1231-40. PMID: 18945961; doi: 10.1182/blood-2008-07-167155.
8. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection - the Maastricht V/Florence Consensus Report. Gut. 2017;66(1):6-30. PMID: 27707777; doi: 10.1136/gutjnl-2016-312288.
9. Braden B. Diagnosis of *Helicobacter pylori* infection. BMJ. 2012;344:e828. PMID: 22368293;. doi: 10.1136/bmj.e828.
10. Obata Y, Kikuchi S, Miwa H, et al. Diagnostic accuracy of serological kits for *Helicobacter pylori* infection with the same assay system but different antigens in a Japanese patient population. J Med Microbiol. 2003;52(Pt 10):889-92. PMID: 12972583; doi: 10.1099/jmm.0.05267-0.
11. Hoang TT, Wheeldon TU, Bengtsson C, et al. Enzyme-linked immunosorbent assay for *Helicobacter pylori* needs adjustment for the population investigated. J Clin Microbiol. 2004;42(2):627-30. PMID: 14766827.
12. Hoang TT, Rehnberg AS, Wheeldon TU, et al. Comparison of the performance of serological kits for *Helicobacter pylori* infection with European and Asian study populations. Clin Microbiol Infect. 2006;12(11):1112-7. PMID: 17002611; doi: 10.1111/j.1469-0691.2006.01514.x.
13. Harris P, Perez-Perez G, Zylberberg A, et al. Relevance of adjusted cut-off values in commercial serological immunoassays for *Helicobacter pylori* infection in children. Dig Dis Sci. 2005;50(11):2103-9. PMID: 16240223; doi: 10.1007/s10620-005-3015-9.
14. Leal YA, Flores LL, García-Cortés LB, Cedillo-Rivera R, Torres J. Antibody-based detection tests for the diagnosis of *Helicobacter pylori* infection in children: A meta-analysis. PLoS One. 2008;3(11):e3751. PMID: 19015732; doi: 10.1371/journal.pone.0003751.
15. Thong-Ngam D, Chayanupatkul M, Vongchampa P, Hanvivatvong O. An evaluation of a new in-house serum and urine ELISA test for detection of *Helicobacter pylori* infection in Thai population. J Med Assoc Thai. 2011;94(8):985-90. PMID: 21863682.
16. Mohammadi M, Talebkhan Y, Khalili G, et al. Advantage of using a home-made ELISA kit for detection of *Helicobacter pylori* infection over commercially imported kits. Indian J Med Microbiol. 2008;26(2):127-31. PMID: 18445947.
17. Aziz F, Taj Y, Kazmi SU. Development of an in-house enzyme-linked immunosorbent assay based on *Helicobacter pylori* sonicate whole cell antigen for diagnosis of gastroduodenal ulcer disease in Karachi, Pakistan. Int J Microbiol Adv Immunol. 2013;1(4):24-31; doi: 10.19070/2329-9967-130005.
18. Ogata SK, Godoy AP, da Silva Patricio FR, Kawakami E. High *Helicobacter pylori* resistance to metronidazole and clarithromycin in Brazilian children and adolescents. J Pediatr Gastroenterol Nutr. 2013;56(6):645-8. PMID: 23403439; doi: 10.1097/MPG.0b013e31828b3669.
19. Smith SI, Oyedeji KS, Arigbabu AO, et al. Comparison of three PCR methods for detection of *Helicobacter pylori* DNA and detection of cagA gene in gastric biopsy specimens. World J Gastroenterol. 2004;10(13):1958-60. PMID: 15222045.
20. Atherton JC, Cao P, Peek RM Jr, et al. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*: Association of specific vacA types with cytotoxin production and peptic ulceration. J Biol Chem. 1995;270(30):17771-7. PMID: 7629077.
21. Van Doorn LJ, Figueiredo C, Sanna R, et al. Clinical relevance of the cagA, vacA, and iceA status of *Helicobacter pylori*. Gastroenterology. 1998;115(1):58-66. PMID: 9649459; doi: 10.1016/S0016-5085(98)70365-8.
22. Perez-Perez GI, Dworkin BM, Chodos JE, Blaser MJ. *Campylobacter pylori* antibodies in humans. Ann Intern Med. 1988;109(1):11-7. PMID: 3288028.

23. Camorlinga-Ponce M, Torres J, Perez-Perez G, et al. Validation of a serologic test for the diagnosis for *Helicobacter pylori* infection and the immune response to urease and Cag A in children. Am J Gastroenterol. 1998;93(8):1264-70. PMID: 9707049; doi: 10.1111/j.1572-0241.1998.00407.x.
24. Khanna B, Cutler A, Israel NR, et al. Use caution with serologic testing for *Helicobacter pylori* infection in children. J Infect Dis. 1998;178(2):460-5. PMID: 9697727.
25. Ogata SK, Kawakami E, Patricio FR, Pedroso MZ, Santos AM. Evaluation of invasive and non-invasive methods for the diagnosis of *Helicobacter pylori* infection in symptomatic children and adolescents. São Paulo Med J. 2001;119(2):67-71. PMID: 11276169.
26. de Oliveira AM, Rocha GA, Queiroz DM, et al. Evaluation of enzyme-linked immunosorbent assay for the diagnosis of *Helicobacter pylori* infection in children from different age groups with and without duodenal ulcer. J Pediatr Gastroenterol Nutr. 1999;28(2):157-61. PMID: 9932847.
27. Rocha GA, Oliveira AM, Queiroz DM, et al. Serodiagnosis of *Helicobacter pylori* infection by Cobas Core ELISA in adults from Minas Gerais, Brazil. Braz J Med Biol Res. 1998;31(10):1263-8. doi: 10.1590/S0100-879X1998001000005.
28. Blaser MJ. Heterogeneity of *Helicobacter pylori*. Eur J Gastroenterol Hepatol. 2012;9 Suppl 1 :S3-6; discussion S6-7. PMID: 22498905.
29. Sunnerstam B, Kjerstadius T, Jansson L, et al. Detection of *Helicobacter pylori* antibodies in a pediatric population: comparison of three commercially available serological tests and one in-house enzyme immunoassay. J Clin Microbiol. 1999;37(10):3328-31. PMID: 10488200.
30. Gatti LL, Módena JL, Payão SL, et al. Prevalence of *Helicobacter pylori* cagA, iceA and babA2 alleles in Brazilian patients with upper gastrointestinal diseases. Acta Trop. 2006;100(3):232-40. PMID: 17181989; doi: 10.1016/j.actatropica.2006.08.014.
31. Lobo Gatti L, Agostinho JNF, De Lábio R, et al. *Helicobacter pylori* and cagA and vacA gene status in children from Brazil with chronic gastritis. Clin Exp Med. 2003;3(3):166-72. PMID: 14648232; doi: 10.1007/s10238-003-0021-0.
32. Widmer M, de Korwin JD, Aucher P, et al. Performance of native and recombinant antigens for diagnosis of *Helicobacter pylori* infection. Eur J Clin Microbiol Infect Dis. 1999;18(11):823-6. PMID: 10614960.
33. Thomas JE, Whatmore AM, Barer MR, Eastham EJ, Kehoe MA. Serodiagnosis of *Helicobacter pylori* infection in childhood. J Clin Microbiol. 1990;28(12):2641-6. PMID: 2279995.
34. Leung WK, Ng EK, Chan FK, Chung SC, Sung JJ. Evaluation of three commercial enzyme-linked immunosorbent assay kits for diagnosis of *Helicobacter pylori* in Chinese patients. Diag Microbiol Infect Dis. 1999;34(1):13-7. PMID: 10342102.

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Cross-sectional epidemiological investigations of *Giardia lamblia* in children in Pakistan

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KEY WORDS:
Prevalence.
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ABSTRACT

BACKGROUND: The prevalence of *Giardia lamblia* in Pakistani children is currently unknown. The aim here was to evaluate the prevalence and risk factors of *Giardia lamblia* in children exhibiting diarrhea.

DESIGN AND SETTING: Cross-sectional study at different district healthcare hospitals in Pakistan.

METHODS: A total of 800 samples were collected from children aged 0-10 years. Information regarding personal data, demographic data and supposed risk factors was collected through a structured questionnaire. *Giardia lamblia* was detected through direct microscopy and antigens through the enzyme-linked immunosorbent assay (ELISA).

RESULTS: The prevalence of *Giardia lamblia* was 2.75% through direct microscopy and inflated to 9.5% through ELISA. The demographic factors positively associated with occurrences of giardiasis were age (P = 0.035; odds ratio, OR = 1.96; 95% confidence interval, CI = 1.094-3.533), mother's educational level (P = 0.031; OR = 2.67; 95% CI = 1.186-6.045) and father's educational level (P = 0.004; OR = 3.56; 95% CI = 1.612-7.899). Similarly, among the supposed risk factors, rural residency (P = 0.032; OR = 1.76; 95% CI = 1.098- 2.851), absence of proper sewerage system (P = 0.000; OR = 6.60; 95% CI = 4.029-10.841) and unavailability of safe drinking water (P = 0.000; OR = 4.08; 95% CI = 2.207-7.547) were the factors strongly connected with giardiasis. Abdominal discomfort was a prominent clinical sign with 46% frequency.

CONCLUSION: Various risk factors were associated with occurrences of *Giardia*, thus emphasizing the importance of parents' education, safe drinking water and proper sewerage systems for Pakistani children's health.

INTRODUCTION

Giardia lamblia, which is also recognized as *Giardia intestinalis* or *Giardia duodenalis*, is the most common protozoon infecting the small intestine of humans and is a major cause of enteric infection throughout the world, especially in children.[1] *Giardia* was first reported by a scientist named Leeuwenhoek in his own stools, in 1681.[2] *G. lamblia* is the only known species of *Giardia* found in humans and other mammals. Seven different genotypes/assemblages (A to G) of *Giardia lamblia* with host specificity have been reported. Assemblages A and B have been reported in humans, cattle and many other mammals.[3] The typical signs of giardiasis include diarrhea, malaise, greasy stools, flatulence, abdominal cramps, bloating and weight loss.[4] Depressed levels of intestinal enzymes and disaccharides are observed, along with absorption defects regarding fat, lactose, vitamin A and vitamin B12.[5]

The life cycle of *Giardia lamblia* involves two stages: trophozoite and cyst. Trophozoites are responsible for producing clinical disease in humans by attaching themselves to the walls of the small intestine, followed by rapid multiplication. On the other hand, cysts are infectious in nature and are responsible for disease transmission. After ingestion of cysts, excystation occurs in the proximal part of the small intestine, resulting in release of trophozoites.[6] *Giardia* cysts are the environmentally stable stage and are resistant to inactivation by various water disinfectants, which makes them viable for up to two months.[3] Transmission of *Giardia* occurs mainly through contaminated water and food. Other factors involved in this include poor living conditions, overcrowded housing, poor environmental sanitation, unhygienic personal habits, unsafe water supply and low socioeconomic class.[7]

The preliminary diagnosis is based on clinical signs presented by children, and it is confirmed through detection of cysts and trophozoites in stool samples by means of direct observation under a microscope, which is considered to be the gold standard for diagnosing *Giardia*.[8] Antigens in stool samples are detected through the enzyme-linked immunosorbent assay (ELISA), which is

currently the most sensitive and most frequently used technique.[9] The prevalence of *Giardia lamblia* is variable: in developed areas of the world, it ranges from 2% to 5%;[10] while in developing countries, the prevalence level is quite high. A major part of this prevalence consists of children under 10 years of age, particularly those who are malnourished.[11]

Although *Giardia lamblia* is considered to be a common zoonotic intestinal parasite in children and adults in Pakistan, the current picture regarding prevalence of *Giardia* in children in Pakistan is still unclear.

OBJECTIVES

The objectives of the present study were to estimate the prevalence of *Giardia lamblia* and identify its possible associated risk factors among children in Pakistan. This was a comprehensive study conducted on children in Pakistan, to assess the predisposing factors for *Giardia* infection.

METHODS

Participants, stool sample collection and settings

Stool samples were collected from children aged 0-10 years exhibiting diarrhea, by means of non-probability-based convenience sampling, between July 2016 and July 2017. The samples were collected from eight healthcare centers (two from each district) located in different districts of Pakistan, including Faisalabad, Khanewal, Multan and Rawalpindi.

A structured questionnaire containing dichotomous questions was designed and was presented to each parent at the time of sample collection from the respective child. The purpose of the questionnaire was to gather information regarding personal details, demographic data and supposed risk factors such as housing and living conditions, contacts with pets and parents' educational level.

A stool sample of 5-10 grams was collected from each child in a sterile plastic container by a trained hospital staff member and was labeled properly. The samples were mixed with 10% formalin and were placed in refrigerator until they were transported to the laboratory, which was done within 24 hours after collection. About half of each sample was used for direct examination under a microscope and the remainder was stored at -80 °C to be used for antigen detection.

Ethical approval

This study was approved by our Institutional Ethics Review Committee under code GCUF/ERC/4155 on April 25, 2016, and the samples were collected in accordance with international safety rules and ethical standards. Written consent was obtained from each parent after they had been given explanations regarding the purpose and objectives of the study.

Detection of *Giardia* in stool samples

The sample obtained from each child was fixed with formalin and a wet-mount was prepared to detect any presence of *Giardia lamblia* (cysts or trophozoites) in the form of a direct smear, using 5% Lugol's iodine and the concentration method.[12]

Detection of *Giardia lamblia* antigen in stool samples

The stool material was subjected to the Ridascreen *Giardia* enzyme immunoassay (R-Biopharm AG, Germany) to detect *Giardia lamblia* antigens, in accordance with the manufacturer's instructions.[13] Positive and negative controls were also run, using test samples. Optical density (OD) was measured using an ELISA reader (Bio-Rad iMark, USA). Positive results were indicated as OD readings that were 10% over the cutoff value, as described in the manufacturer's instructions.

Statistical analysis

The data obtained were tabulated in a Microsoft Excel spreadsheet and were analyzed using STATA version 12 (Stata Corp., USA). Descriptive analysis was used to summarize the data on the basis of percentages and chi-square tests. In the present study, stool samples were considered positive for *Giardia lamblia* if any of the tests were positive.

Bivariate analysis was conducted to establish associations between risk factors and presence of giardiasis in children. Odds ratios (OR) were calculated at 95% confidence intervals (CI).[9] P-values < 0.05 were considered to be statistically significant.

RESULTS

The present study involved 800 children who were evaluated during the study period due to diarrhea, comprising 412 males (51.50%) and 388 females (48.50%) ranging in age from 0 to 10 years. On the basis of age, the children were divided into two groups: 0-5 years (n = 549) and 6-10 years (n = 251).

The results from our study showed that out of the total of 800 samples, 22 (2.75%) were positive for giardiasis according to the direct method under a microscope. The ELISA test showed prevalence of 8.88%, through detecting *Giardia lamblia* in 71 samples. Five samples were found to be negative according to ELISA but were positive through direct examination under a microscope. Similarly, 30 samples were found to be negative through direct examination but were positive according to ELISA. Thus, the overall prevalence of *Giardia lamblia* infection was 9.5%, i.e. 76/800 samples were positive.

The prevalence of *Giardia lamblia* was non-significantly different on the basis of geographical location (P = 0.278). It was found to be highest (12.5%) in the Khanewal district, while the lowest prevalence was observed in the Faisalabad district (6.5%), as shown in **Table 1**. On the basis of area of residence, it was

recorded that children living in rural areas were more prone to *Giardia lamblia* infection than were those living in urban areas. Statistically, these results were also significant [P = 0.032; OR = 1.76; 95% CI = 1.098- 2.851]. Conversely, children living in houses with proper sewerage and drainage systems were well protected from this infection [P = 0.000; OR = 6.60; 95% CI = 4.029-10.841], as also were those who had the facility of proper drinking water and a water supply system, who also had very small chances of getting this infection [P = 0.000; OR = 4.08; 95% CI = 2.207-7.547].

On the basis of gender, the prevalences of giardiasis in male and female children were 11.40% (47/412) and 7.5% (29/388), respectively. Statistically, there was no significant variation in the prevalence of *Giardia* with regard to gender (P > 0.05).

A significant difference in the prevalences of *Giardia lamblia* was found between the children in the two age groups. The rate of susceptibility to giardiasis was higher (11.11%) among the children in the age range 0-5 years than among those in the age range 6-10 years (5.97%) [P = 0.035; OR = 1.96; 95% CI = 1.094-3.533], as shown in **Table 2**.

The parents' educational level was significantly associated with the prevalence of giardiasis among children. The children of uneducated mothers were more likely to have *Giardia lamblia* infection than were those of educated mothers [P = 0.031; OR = 2.67; 95% CI = 1.186-6.045]. Similarly, children whose fathers had not had any education were 3.5 times more at risk of being infected with *Giardia lamblia* than were those whose fathers had received education [P = 0.004; OR = 3.56; 95% CI = 1.612-7.899], as shown in (**Table 2**).

The percentages were found to be variable among the groups of different suspected risk factors, but statistically there was no association between the prevalence of giardiasis and some variables like birth order, number of children, attendance at a day care center, living in a house versus in an apartment, availability of washrooms and presence of pets at home (**Table 3**). The predominant clinical presentations among the children infected with *Giardia lamblia* were abdominal pain and discomfort (46%), vomiting (13.15%) and bloody diarrhea (10.52%).

DISCUSSION

The present study determined the prevalence of *Giardia lamblia* infection among children in different districts of Punjab, Pakistan, and the potential risk factors associated with occurrences of

Table 2. Prevalence of *Giardia lamblia* among children, according to demographic characteristics

Risk factors	n	Positive (%)	P-value	Odds ratio	95% confidence interval
Gender (n = 800)					
Male	412	47 (11.40%)	0.084	1.59	(0.981-2.589)
Female	388	29 (7.50%)			
Age (n = 800)					
0-5 years	549	61 (11.11%)	0.035	1.96	(1.094-3.533)
6-10 years	251	15 (5.97%)			
Birth order (n = 788)					
Not first	73	8 (10.95%)	0.718	1.17	(0.539-2.543)
First	715	68 (9.51%)			
No. of children (n = 800)					
One	355	27 (7.60%)	0.137	1.50	(0.919-2.458)
More than one	445	49 (11.01%)			
Mother's education (n = 785)					
Not educated	42	8 (19.05%)	0.031	2.67	(1.186-6.045)
Educated	743	60 (8.08%)			
Father's education (n = 763)					
Not educated	38	9 (23.70%)	0.004	3.56	(1.612-7.899)
Educated	725	58 (8.00%)			
Day care center (n = 800)					
Yes	188	21 (11.17%)	0.419	1.27	(0.748-2.167)
No	612	55 (8.99%)			

Table 3. Prevalence of *Giardia lamblia* among children, according to housing characteristics

Risk factors	n	Positive (%)	P-value	Odds ratio	95% confidence interval
Residence (n = 800)					
Rural	350	43 (12.28%)	0.032	1.769	(1.098-2.851)
Urban	450	33 (7.33%)			
Housing (n = 800)					
Apartment	285	31 (10.87%)	0.370	1.274	(0.787-2.064)
House	515	45 (8.73%)			
Sewerage system (n = 800)					
Yes	650	35 (5.38%)	0.000	6.604	(4.029-10.841)
No	150	41 (27.33%)			
Bathroom (n = 800)					
Yes	705	62 (8.79%)	0.098	1.792	(0.960-3.346)
No	95	14 (14.73%)			
Drinking water system (n = 800)					
Yes	344	13 (3.77%)	0.000	4.08	(2.207-7.547)
No	456	63 (13.81%)			
Pets (n = 800)					
Yes	80	11 (13.75%)	0.222	1.60	(0.809-3.188)
No	720	65 (9.03%)			

Table 1. Prevalence of *Giardia lamblia* among children in different districts in Pakistan

Area	Male		Female		Total	
	Total sampled	Total positive (percentage)	Total sampled	Total positive (percentage)	Total sampled	Total positive (percentage)
Faisalabad	104	8 (7.7%)	96	5 (5.2%)	200	13 (6.5%)
Multan	109	13 (11.9%)	91	8 (8.8%)	200	21 (10.5%)
Khanewal	101	17 (16.8%)	99	8 (7.8%)	200	25 (12.5%)
Rawalpindi	98	9 (9.2%)	102	8 (8.1%)	200	17 (8.5%)
Total	412	47 (11.40%)	388	29 (7.5%)	800	76 (9.5%)

giardiasis. This type of epidemiological study has routinely been conducted by using direct examination under a microscope or by using an immunochromatographic test (ICT), because the latter method is more cost-effective and less time-consuming. However, the low sensitivity of this test results in inaccurate data regarding the prevalence of this disease.

In the current study, direct examination under a microscope and the enzyme-linked immunosorbent assay (ELISA) were used in combination to detect the current prevalence of giardiasis. The overall prevalence of *Giardia lamblia* was found to be 9.5%. On the basis of area, the difference in the prevalence of *Giardia* was found to be non-significant, which is an indication that the disease is equally prevalent in geographically different districts. The results from our study greatly resemble the findings from other studies of 11.8% prevalence in Pakistan,[14] 9% in Kabul[6] and 6.8% in Portugal.[9] Much higher levels of *Giardia* occurrence were observed among Afghan refugees (37.7%)[12] and in Guatemala (43.8%).[15] This variation in the prevalence of *Giardia lamblia* is probably due to differences in socioeconomic level between countries. Prevalences range from 2% to 7% in industrial countries and reach up to 40% in developing countries.[16]

The current study revealed that the prevalence of *Giardia* infection was 11.11% among children aged 0-5 years and 5.97% among those aged 6-10 years. These results were in accordance with previous findings from Julio et al.[9] and Baido et al.[17] A higher level of prevalence (31.9%) was reported in Russia among children aged 0-5 years.[18] This may have been due to lack of acquired immunity among these children.[19] The rate of positivity for *Giardia* in our study was almost equal between the sexes, and this was also seen in several previous studies.[17,20,21] The presence of intestinal parasites in children results from some constant factors like food quality, water supply, personal and community hygiene, climate, sanitation conditions, proximity to domestic and wild animals and socioeconomic condition.[22]

The results from the present study revealed that the lower the mother's educational level was, the higher the risk of *Giardia lamblia* infection. This finding is strengthened by the results from previous studies conducted in Pakistan,[14] Malaysia,[23] Tehran[24] and Mexico.[25] Similarly, it was also observed that the father's educational level was inversely related to the risk of *Giardia lamblia* infection, and this is also supported by findings from previous research.[9] This might be due to the fact that the father's educational level is also reflected in socioeconomic status, such that lower status leads to poorer hygiene and sanitary conditions.

People living in rural areas showed higher levels of *Giardia intestinalis* infection than what was seen among people living in urban areas. This is also supported by data from previous studies, which showed that people living in rural areas had three times more chance of having giardiasis.[25,26] Likewise, there was an inverse relationship between presence of a sewerage system and occurrence of *Giardia* infections. Similar results have also been recorded in many other studies.[9,26] The reasons for this finding might be lack of sanitary and hygiene facilities in rural areas, as compared with urban areas, along with differences in awareness regarding the disease.

Drinking water is one of the major necessities of life and, if contaminated, it is a potential cause of many bacterial and parasitic diseases. In the present study, it was found that the prevalence of *Giardia lamblia* is greatly elevated among children who used untreated/unfiltered water, compared with the prevalence among those who used filtered or treated water for drinking purposes. The chances of infection if untreated water is used are four times greater.[9,26] Attendance at day care centers among the children, unavailability of bathrooms and having pets at home increased the prevalence of *Giardia lamblia* infection among the children in our study, but these results were not statistically significant.

CONCLUSION

The findings from this study showed that the prevalence of *Giardia lamblia* is still high and is an issue of public health concern. The factors strongly associated with occurrences of giardiasis were the parents' educational level, lack of a bathroom, lack of sewerage facilities and unsafe drinking water. These findings indicate that improving these factors will have a positive impact on the wellbeing of Pakistani children. Further detailed studies at national level are needed regarding the epidemiology and burden of giardiasis, and the financial losses that it causes, in order to devise better control measures.

REFERENCES

1. Ali SA, Hill DR. Giardia intestinalis. Curr Opin Infect Dis. 2003;16(5):453-60. PMID: 14501998; doi: 10.1097/01.qco.0000092817.64370.ab.
2. Adam, RD. Biology of Giardia lamblia. Clin Microbiol Rev. 2001;14(3): 447-75. PMID: 11432808; doi: 10.1128/CMR.14.3.447-475.2001.
3. Thompson RC. Giardiasis as a re-emerging infectious disease and its zoonotic potential. Int J Parasitol. 2000;30(12-13):1259-67. PMID: 11113253; doi: 10.1016/S0020-7519(00)00127-2.
4. Thompson RC. The zoonotic significance and molecular epidemiology of Giardia and giardiasis. Vet Parasitol. 2004;126(1-2):15-35. PMID: 15567577; doi: 10.1016/j.vetpar.2004.09.008.
5. Lengerich EJ, Addiss DG, Juranek DD. Severe giardiasis in the United States. Clin Infect Dis. 1994;18(5):760-3. PMID: 8075266; doi: 10.1093/clinids/18.5.760.
6. Tariq MT. Prevalence of Giardiasis in Afghan population. Pak Pediatr J. 2013;37(3):180-4. Available from: https://www.researchgate.net/publication/287318505_Prevalence_of_Giardiasis_in_Afghan_Population. Accessed in 2018 (Aug 24).
7. Savioli L, Smith H, Thompson A. Giardia and Cryptosporidium join the 'Neglected Diseases Initiative'. Trends Parasitol. 2016;22(5):203-8. PMID: 16545611; doi: 10.1016/j.pt.2006.02.015.

8. Mank TG, Zaat JO, Deelder AM, et al. Sensitivity of microscopy versus enzyme immunoassay in the laboratory diagnosis of giardiasis. Eur J Clin Microbiol Infect Dis. 1997;16(8):615-9. PMID: 9323478; doi: 10.1007/BF02447929.
9. Julio C, Vilares A, Oleastro M, et al. Prevalence and risk factors for Giardia duodenalis infection among children: a case study in Portugal. Parasit Vectors. 2012;5:22. PMID: 22284337; doi: 10.1186/1756-3305-5-22.
10. Oberhuber G, Kastner N, Stolte M. Giardiasis: a histologic analysis of 567 cases. Scand J Gastroenterol. 1997;32(1):48-51. PMID: 9018766; doi: 10.3109/00365529709025062.
11. Al-Mekhlafi MS, Azlin M, Nor Aini U, et al. Giardiasis as a predictor of childhood malnutrition in Orang Asli children in Malaysia. Trans R Soc Trop Med Hyg. 2005;99(9):686-91. PMID: 15992838; doi: 10.1016/j.trstmh.2005.02.006.
12. Abrar Ul Haq K, Gul NA, Hammad HM, et al. Prevalence of Giardia intestinalis and Hymenolepis nana in Afghan refugee population of Mianwali district, Pakistan. Afr Health Sci. 2015;15(2):394-400. PMID: 26124784; doi: 10.4314/ahs.v15i2.12.
13. Korzeniewski K, Konior M, Augustynowicz A, Lass A, Kowalska E. Detection of Giardia intestinalis infections in Polish soldiers deployed to Afghanistan. Int Marit Health. 2016;67(4):243-7. PMID: 28009386; doi: 10.5603/IMH.2016.0043.
14. Chaudhry ZH, Afzal M, Malik MA. Epidemiological factors affecting prevalence of intestinal parasites in children of Muzaffarabad district. Pakistan J Zool. 2004;36(4):267-71. Available from: https://zsp.com.pk/pdf36/PJZ-165-03.pdf. Accessed in 2018 (Aug 24).
15. Duffy T, Montenegro-Bethancourt G, Solomons NW, Belosevic M, Clandinin MT. Prevalence of giardiasis in children attending semi-urban day care centres in Guatemala and comparison of 3 Giardia detection tests. J Health Popul Nutr. 2013;31(2):290-3. PMID: 23930348; doi: 10.3329/jhpn.v31i2.16394.
16. Upcroft P. Meeting report: Anaerobic Protozoan Parasites, Prague, Czech Republic, July 15-19, 2001. Protist. 2001;152(4):241-2. PMID: 11822654; doi: 10.1078/1434-4610-00000.
17. Anim-Baidoo I, Narh CA, Oddei D, et al. Giardia lamblia infections in children in Ghana. Pan Afr Med J. 2016;24:217. PMID: 27800072; doi: 10.11604/pamj.2016.24.217.8012.
18. Kramar LV, Reznikov EV, Kramar OG. [Prevalence of giardiasis in Volgograd city population]. Med Parazitol (Mosk). 2003;(4):38-9. PMID: 14727490.
19. Wongstitwilairoong B, Srijan A, Serichantalergs O, et al. Intestinal parasitic infection among pre-school children in Sangkhlaburi, Thailand. Am J Trop Med Hyg. 2007;76(2):345-50. PMID: 17297047; doi: 10.4269/ajtmh.2007.76.345.
20. Abbas NF, El-Shaikh KA, Almohammady MS. Prevalence of Giardia lamblia in diarrheic children in Almadinah Almunawarh, KSA. J Taib Uni Sci. 2011;5:25-30. doi: 10.1016/S1658-3655(12)60035-1.
21. Suman MSH, Alam MM, Pun SB, et al. Prevalence of Giardia lamblia infection in children and calves in Bangladesh. Bangl J Vet Med. 2011;9(2):177-82. doi: 10.3329/bjvm.v9i2.13474.
22. Reinthaler FF, Feierl G, Stünzner D, Marth E. Diarrhea in returning Austrian tourists: epidemiology, etiology, and cost analyses. J Travel Med. 1998;5(2):65-72. PMID: 9772320; doi: 10.1111/j.1708-8305.1998.tb00466.x.
23. Choy SH, Al-Mekhlafi HM, Mahdy MA, et al. Prevalence and associated risk factors of Giardia infection among indigenous communities in rural Malaysia. Sci Rep. 2014;4:6909. PMID: 25366301; doi: 10.1038/srep06909.
24. Nematian J, Nematian E, Gholamrezanezhad A, Asgari AA. Prevalence of intestinal parasitic infections and their relation with socio-economic factors and hygienic habits in Tehran primary school students. Acta Trop. 2004;92(3):179-86. PMID: 15533285; doi: 10.1016/j.actatropica.2004.06.010.
25. Quihui L, Valencia ME, Crompton DW, et al. Role of the employment status and educational of mothers in the prevalence of intestinal parasitic infections in Mexican rural schoolchildren. BMC Public Health. 2006;6:225. PMID: 16956417; doi: 10.1186/1471-2458-6-225.
26. Bello J, Núñez FA, González OM, et al. Risk factors for Giardia infection among hospitalized children in Cuba. Ann Trop Med Parasitol. 2011;105(1):57-64. PMID: 21294949; doi: 10.1179/136485911X12899838413385.

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Temporal trends in the nutritional status of women and children under five years of age in sub-Saharan African countries: ecological study

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ABSTRACT

BACKGROUND: While the global prevalence of obesity is rapidly increasing, this pandemic has received less attention in sub-Saharan Africa, particularly in the light of the persistent undernutrition that exists in the context of maternal and child health. We aimed to describe obesity trends among women of childbearing age over recent decades, along with trends in over and undernutrition among children under five years of age, in sub-Saharan African countries.

DESIGN AND SETTING: Ecological study with temporal trend analysis in 13 sub-Saharan African countries.

METHODS: This was a description of temporal trends in nutritional status: adult obesity, childhood overweight, low height-for-age (stunting), low weight-for-height (wasting), low weight-for-age (underweight) and low birth weight. Publicly available data from repeated cross-sectional national surveys (demographic and health surveys and multiple-indicator cluster surveys) were used. We chose 13 sub-Saharan African countries from which at least four surveys conducted since 1993 were available. We investigated women aged 15-49 years and children under five years of age.

RESULTS: In multilevel linear models, the prevalence of obesity increased by an estimated 6 percentage points over 20 years among women of childbearing age, while the prevalence of overweight among children under 5 years old was stable. A major decrease in stunting and, to a lesser extent, wasting accompanied these findings.

CONCLUSIONS: The upward trend in obesity among women of childbearing age in the context of highly prevalent childhood undernutrition suggests that the focus of maternal and child health in sub-Saharan Africa needs to be expanded to consider not only nutritional deficiencies but also nutritional excess.

INTRODUCTION

Obesity, a complex condition that affects all ages and socioeconomic groups, has become one of the world's most challenging public health problems. Because it has been raising the prevalence of non-communicable diseases in low and middle-income countries that are still burdened with infections and nutritional deficiencies, it has helped to create a "double burden" of disease that threatens to overwhelm healthcare services.[1-3] Its prevalence is increasing rapidly worldwide, and this trend is believed to be related to dietary excess, physical inactivity[4] and increasing urbanization.[5]

Childhood overweight has also been increasing at an alarming rate. This is defined in accordance with the World Health Organization child growth standards as a weight-for-height z-score ≥2 standard deviations above the median of the reference population.[6] Its worldwide prevalence increased from 4.2% (95% confidence interval, CI, 3.2%-5.2%) in 1990 to 7.8% (95% CI, 6.4%-9.1%) in 2015. This trend is expected to reach 9.1% (95% CI, 7.3%-10.9%) in 2020.[7] Currently, at least 41 million children under five years of age are obese or overweight, and the greatest rise is being seen in low and middle-income countries.[7] In Africa, the number of overweight children rose from 5 million in 1990 to 10 million in 2014.[8]

While tackling obesity is a current public health priority in most of the world, in sub-Saharan Africa the issue has received less attention, especially within the context of maternal and child health. In this region, the main nutritional concern continues to be undernutrition, particularly among children.

Most data available on the nutritional situation in sub-Saharan African countries are derived from standardized national surveys. However, to our knowledge, no studies focusing on sub-Saharan

Africa have investigated trends using nationally representative data from several of these countries to characterize trends in excess weight among women of childbearing age and children under five years of age.

The aim of the present study was thus to describe obesity trends among women of childbearing age and overweight trends among children under five, over the past two decades, within the context of the continuing general picture of undernutrition among young children living in sub-Saharan Africa.

METHODS

To determine temporal trends regarding the prevalence of over and undernutrition in sub-Saharan African countries, we analyzed secondary data from demographic and health surveys (DHS).[9] These are nationally representative surveys of sizes ranging from 5,000 to 30,000 households that were funded by the United States Agency for International Development (USAID). They were usually conducted every five years to collect data on several topics from selected countries.

Standard data collection procedures and manuals had been used to guide the household survey process, and the data had been processed and presented in reports that described the situation in each country. We also used secondary data from multiple indicator cluster surveys (MICS),[10] which are nationally representative cross-sectional household surveys that were funded by the United Nations Children's Fund (UNICEF). These were conducted on an average of 11,000 households and provided information about maternal and child health.

For the present study, the sub-Saharan African countries from which at least four surveys providing information on the prevalence of obesity in women and/or anthropometric data on children under five years of age had been conducted since the early 1990s were eligible for inclusion. Thirteen countries were thus eligible, from which a total of 60 MICS or DHS conducted between 1993 and 2014 were available.

In the DHS, objective height and weight measurements had been made on women aged 15-49 years and on children under five years of age. Height had been measured using portable stadiometers. For children up to the age of two years, height had been measured in a lying position. Weight had been measured using portable digital scales.[11] In MICS, similar direct measurements had been made on children, but maternal height and weight had not been obtained.[10] Thus, the data on obesity among women of childbearing age for this study came only from the DHS.

Women were classified as obese if their body mass index was ≥ 30 kg/m^2. In separate analyses, children under five years of age were classified with regard to wasting (low weight-for-height), stunting (low height-for-age), underweight (low weight-for-age) and overweight (high weight-for-height). These were based on z-scores for height and weight that were calculated in accordance with the World Health Organization child growth standards.[6] Wasting, stunting and underweight were defined as two or more standard deviations below the median and overweight as two or more standard deviations above the median of the reference population.[12] Birth weight had been obtained through interviews with parents/guardians for children under two years of age. Low birth weight was defined as < 2500 g,[13] which is a birth weight below the third percentile, according to the World Health Organization child growth standards.

Prevalence rates, with their respective confidence intervals, were estimated for each country at each point in time, using weighting to account for aspects of the survey design, including cluster effects,[14] in order to obtain nationally representative estimates of the population. For each indicator, temporal trends were plotted as line graphs using Microsoft Excel 2010, with one line per country. To facilitate graphical presentation of the data, the eligible countries were divided into four arbitrary groups as follows:

1. west (north): Burkina Faso, Mali, Senegal and Ivory Coast;
2. west (south): Ghana, Nigeria and Cameroon;
3. east (north): Kenya, Tanzania and Uganda; and
4. east (south): Malawi, Mozambique and Zimbabwe.

For trend analysis, estimated temporal trends were obtained for each outcome per country and for the group of 13 countries combined. Annual changes were estimated by means of linear regression using variance-weighted least squares of the values observed in each survey versus time elapsed from the first survey, using Stata, version 13.0.

Overall temporal trends regarding the prevalence of the different outcomes in the 13 countries were analyzed using a two-level hierarchical linear model. In this model, the country was the contextual variable, and both the intercept and the slope coefficient were treated as random variables. This analysis was also performed using Stata, version 13.0. Given the diversity of settings both among the countries included and among those not included in this study, we felt that treating these countries as random representatives of the sub-Saharan region was the best approach. Thus, this analysis was performed without additional weighting for country size.

All analyses were based on publicly available data from national surveys. Ethical clearance was the responsibility of the institutions that administered those surveys.

RESULTS

The trends regarding the prevalence of obesity among women aged 15-49 years are shown in **Table 1** and **Figure 1**, **Panel A**. A strong upward trend in obesity can be seen among women of childbearing age in most countries, especially in Cameroon, Ghana and Kenya, with increases of 0.55, 0.48 and 0.35 percentage points per year (pp/yr), respectively ($P < 0.001$). In recent

Table 1. Trend analysis regarding obesity among women 15-49 years of age and regarding overweight and stunting among children under five years of age in 13 sub-Saharan African countries

Country	N	Prev	Last year	Change		P
				pp/yr	95% CI	
Obesity						
Burkina Faso	3	0.031	2010	0.187	0.140-0.233	< 0.001
Cameroon	3	0.107	2011	0.550	0.454-0.646	< 0.001
Ivory Coast	3	0.066	2011	0.207	0.134-0.281	< 0.001
Ghana	5	0.153	2014	0.477	0.408-0.546	< 0.001
Malawi	3	0.040	2010	0.175	0.106-0.244	< 0.001
Mali	4	0.051	2012	0.246	0.201-0.291	< 0.001
Mozambique	3	0.042	2011	0.152	0.092-0.212	< 0.001
Nigeria	4	0.075	2013	0.118	0.042-0.194	0.002
Kenya	4	0.072	2008	0.347	0.273-0.422	< 0.001
Senegal	2	0.058	2010	-0.285	-0.582-0.011	0.059
Tanzania	3	0.062	2010	0.258	0.191-0.325	< 0.001
Uganda	4	0.042	2011	0.215	0.153-0.277	< 0.001
Zimbabwe	4	0.106	2010	0.240	0.158-0.323	< 0.001
Overweight among children						
Burkina Faso	4	0.031	2010	0.088	0.024-0.152	0.007
Cameroon	3	0.082	2011	-0.441	-0.658-0.224	< 0.001
Ivory Coast	3	0.043	2011	-0.270	-0.404-0.136	< 0.001
Ghana	6	0.027	2014	-0.033	-0.091-0.026	0.275
Malawi	4	0.113	2010	0.069	-0.081-0.190	0.428
Mali	3	0.034	2012	0.020	-0.055-0.096	0.600
Mozambique	3	0.095	2011	0.132	-0.022-0.286	0.092
Nigeria	5	0.051	2013	-0.775	-0.881-0.669	< 0.001
Kenya	3	0.062	2008	-0.059	-0.145-0.027	0.176
Senegal	4	0.014	2014	-0.168	-0.270-0.067	0.001
Tanzania	4	0.064	2010	0.087	0.014-0.159	0.019
Uganda	4	0.051	2011	0.081	-0.159-0.003	0.041
Zimbabwe	5	0.050	2014	-0.507	-0.585-0.429	< 0.001
Stunting among children						
Burkina Faso	4	0.346	2010	-0.622	-0.807-0.437	< 0.001
Cameroon	3	0.325	2011	-0.573	-0.924-0.222	0.001
Ivory Coast	3	0.297	2011	-0.235	-0.520-0.051	0.107
Ghana	9	0.188	2014	-0.922	-1.070-0.774	< 0.001
Malawi	4	0.471	2010	-0.574	-0.793-0.355	< 0.001
Mali	3	0.383	2012	-0.354	-0.592-0.116	0.004
Mozambique	3	0.426	2011	-0.565	-0.848-0.282	< 0.001
Nigeria	5	0.368	2013	-0.629	-0.848-0.411	< 0.001
Kenya	3	0.353	2008	-0.329	-0.512-0.145	< 0.001
Senegal	4	0.187	2014	-0.258	-0.554-0.039	0.089
Tanzania	4	0.420	2010	-0.544	-0.725-0.363	< 0.001
Uganda	4	0.334	2011	-0.740	-0.920-0.560	< 0.001
Zimbabwe	5	0.276	2014	-0.456	-0.602-0.310	< 0.001

N = total number of surveys; pp/yr = annual percentage point change in the indicator; CI = confidence interval. Prev = prevalence at the end of the series (most recent year).

surveys, the prevalence of obesity among these women ranged from 3% in Burkina Faso (in 2010) to 15% in Ghana (in 2014).

Trends regarding the prevalence of overweight among children under five years of age are also shown in **Table 1** and in **Figure 1**, **Panel B**. Differences in trends between countries were evident: while some countries showed an increase in overweight among children under five, other countries showed a downward trend. Thus, there was no evident overall trend. High prevalence rates were observed in a few countries at the end of the series: 8% in Cameroon (in 2011), 11% in Malawi (in 2009) and 10% in Mozambique (in 2011).

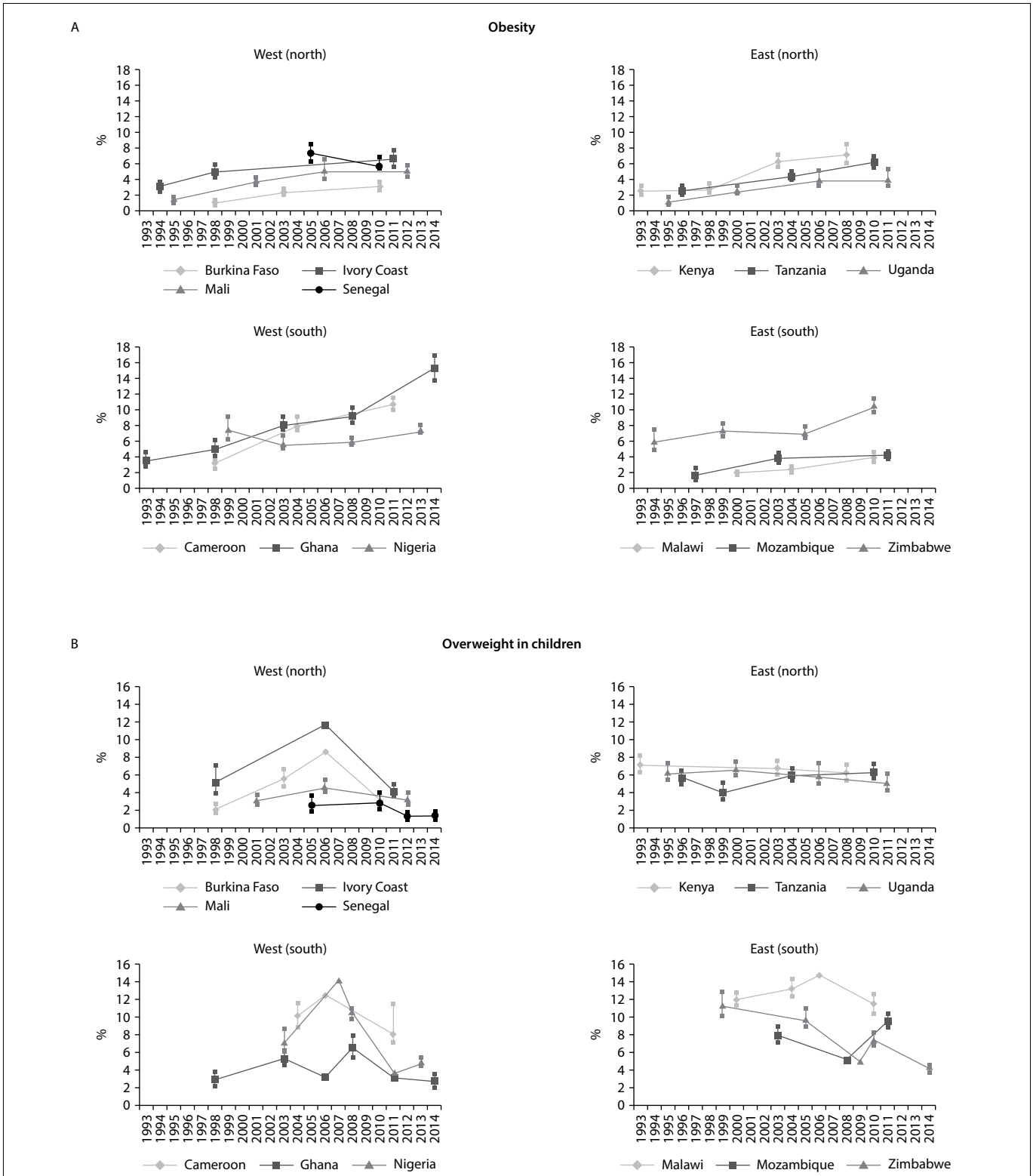
A strong downward trend in stunting prevalence, frequently greater than 0.5 pp/yr, was observed in the sub-Saharan region (**Table 1**; **Figure 1**, **Panel C**). However, despite this downward trend, the prevalence rates for stunting were still high in most countries at the end of the series and were particularly notable in Nigeria, at 37% in 2013; Mali, at 38% in 2012; Tanzania, at 41% in 2010; Malawi, at 47% in 2010; and Mozambique, at 42% in 2011.

The trends in the prevalence of wasting among children under five years of age are shown in **Table 2** and **Figure 2**, **Panel A**. Most of the countries showed small downward changes, ranging from -0.01 to -0.31 pp/yr, indicating slight improvement. However, high prevalence rates were observed at the end of the series in some countries, most notably Nigeria (17%) and Burkina Faso (15%).

Large trends with regard to underweight in children were observed in most countries in the sub-Saharan region, many decreasing more than -0.4 pp/yr (**Table 2**; **Figure 2**, **Panel B**). However, as with the above indicators, high rates of underweight were observed at the end of the series in some countries, with prevalence rates of more than 20% in Burkina Faso and Mali and almost 30% in Nigeria.

Regarding low birth weight (**Table 2**; **Figure 2**, **Panel C**), irregular annual variations characterized the trends. Some countries showed an upward trend, most notably Malawi and Senegal, with annual changes in this indicator of 0.1 and 0.2 pp/yr, respectively ($P < 0.05$). Prevalence rates of approximately 10% were common at the end of the series.

Table 3 summarizes the results in terms of overall tendencies based on the multilevel linear models, including all 13 countries, studied as a group. Over the period from 1993 to 2014, an average increase in obesity of 0.3 pp/yr was observed among women (or 6 percentage points over 20 years; $P < 0.001$), while the prevalence of overweight among the under-five children remained almost unchanged (up by 0.11 pp/yr; $P = 0.14$). There were significant improvements in stunting (at a mean of −0.52 pp/yr; $P < 0.001$) and underweight (at a mean of −0.32 pp/yr; $P < 0.001$). However, the other indicators of undernutrition remained basically unchanged, such that the mean change of wasting was −0.11 pp/yr; $P = 0.09$) and the mean change in low birth weight was −0.03 pp/yr; $P = 0.30$).



Sources: demographic and health surveys (DHS) (http://www.measuredhs.com/aboutsurveys/dhs/star.cfm) and multiple indicator cluster surveys (MICS) (http://www.childinfo.org/).

Figure 1. Panel A. Trends in obesity among women 15-49 years of age in 13 sub-Saharan African countries. Panel B. Trends in overweight among children under five years of age in 13 sub-Saharan African countries. Panel C. Trends in stunting among children under five years of age in 13 sub-Saharan African countries.

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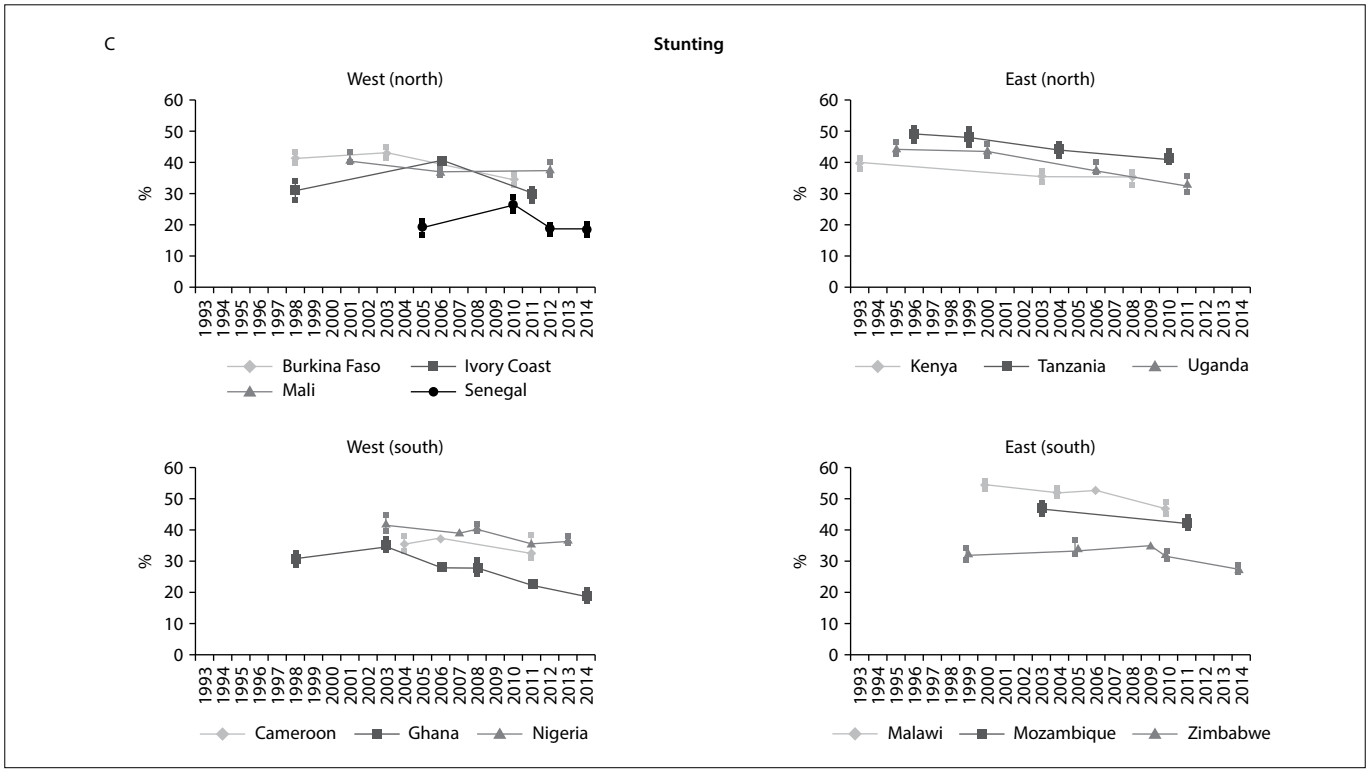

Figure 1. Continuation.

A sensitivity analysis was performed within the evaluation of overall trends to investigate the effect of weighting the data so as to reflect the sizes of the different countries. The results were in the same direction and of similar magnitude, such that the increase in obesity among women was slightly lower (0.22 pp/yr), while the trend in childhood overweight was unchanged (0.11 pp/yr). The decline in stunting was slightly higher (−0.56 pp/yr), while the decrease in wasting was somewhat lower (−0.19 pp/yr). The decline in underweight was lower (−0.19 pp/yr) and not statistically significant, while the decrease in low birth weight was slightly higher (−0.09 pp/yr) and statistically significant (P = 0.02).

DISCUSSION

In the present study, we describe a significant increase in the prevalence of obesity among sub-Saharan African women aged 15-49 years, with a rise in absolute terms of 5.6 pp over 20 years. Additionally, considering countries with at least three surveys, we found marked differences in the degree of change between countries, from 2.5 pp in Nigeria to 7.0 pp in Cameroon. The prevalence of obesity reported for these women in the most recent surveys in each country ranged from 3% to 15%.

Over the same period, the prevalence of overweight among children under five years of age lacked a clear overall trend, with an estimated average increase of only 2.0 pp over 20 years. In contrast, the prevalence of stunting decreased notably over the same period, on average by 10.3 pp. Despite this decline, the prevalence rates for stunting remained excessively high (15) (e.g. 47% and 42%, in Malawi and Mozambique, respectively). Despite the irregular trend in wasting, improvements were observed over time, as shown by the statistically significant downward trends in several countries. The prevalence of underweight also decreased significantly, down by an estimated mean of 6.5 pp over the 20-year period. Finally, favorable trends in birth weight were present in some countries, especially Kenya and Tanzania, despite the lack of improvement overall.

Within this overall picture, our findings of obesity among women are consistent with those reported by others who investigated temporal trends in overweight among women and children in low and middle-income countries using DHS. Jaacks et al. examined recent trends among women aged 19-49 years living in rural and urban areas in 33 low and middle-income countries[16] and showed that the prevalence of overweight increased significantly in almost all countries. The increase has been most notably among urban women: 5 pp in Africa, 6 pp in the Americas and 4 pp in Asia between 1990 and 2011.[17] The increase in prevalence reported for Africa was close to that found in the present study (5.6%), in which we considered both rural and urban areas together. Although Jones-Smith et al.[18] observed that the prevalence of being

overweight had a positive relationship with wealth and education, they noted that the rate of weight gain over time was frequently greater in groups of lower socioeconomic status. Razak et al.[19] reported that, while populations as a whole are gaining weight, the pattern of these gains is not uniform across the range of body mass indexes. The main increases were found to be concentrated in the overweight and obese parts of the spectrum, while there was frequently little or no change in the underweight and normal-weight parts of the nutritional status distribution.

Focusing on children and adolescents (aged < 20) in developing countries, Ng et al.[20] reported major increases in the prevalence of obesity. Thus, they suggested that once the first years of life have passed, many sub-Saharan African children manifest the result of their now obesogenic environment.

Although our findings regarding overweight in children under five years of age did not show any major trend overall, the prevalence was quite heterogeneous across nations. Some countries already had significant proportions of overweight children at the end of the period studied, whereas in others the prevalence changed little over the last two decades. Additionally, low rates of overweight in early childhood did not prevent higher rates shortly thereafter, as the previously mentioned findings of Ng et al. showed.

Although recent levels of stunting remain unacceptably high in most of the countries studied, the decline in stunting, which is a major cause of morbidity and mortality among children under five years of age,[21-23] is a strong indicator that a transition in the nutritional status of under-five children is in course in sub-Saharan Africa.

The current data, within the context of the obesity pandemic and of recent trends in other developing nations,[20] suggest that probable future improvements in indicators of childhood undernutrition in sub-Saharan Africa will be accompanied by progressive increases in childhood overweight and obesity in coming years. Moreover, the data suggest that high rates of overweight and obesity among sub-Saharan African adolescents and adults within a few decades are quite likely, even among those whose childhood was marked by wasting and stunting. Additionally, these high rates will most likely soon be accompanied by high rates of obesity-related complications, especially diabetes.

Additionally, studies have suggested that gestational diabetes, which frequently accompanies obesity during pregnancy, also increases these risks.[24] Pre-pregnancy obesity and gestational diabetes are major risk factors for large-for-gestational-age births,[25,26] and the risk of adult obesity is uniformly greater among those born with excess weight.[27] This is notably so in the context of a rapid nutritional transition.[28] Within the conceptual framework of the developmental origins of health and disease, several noncommunicable diseases originate in the fetal period and during early life.[27,29,30] These facts highlight how important it is for sub-Saharan

Table 2. Trend analysis regarding wasting, underweight and birth weight among children under five years of age in 13 sub-Saharan African countries

Country	N	Prev	Last year	Change		P
				pp/yr	95% CI	
Wasting among children						
Burkina Faso	4	0.154	2010	-0.060	-0.217-0.097	0.454
Cameroon	3	0.056	2011	-0.132	-0.280-0.016	0.081
Ivory Coast	3	0.076	2011	0.078	-0.068-0.225	0.295
Ghana	6	0.047	2014	-0.290	-0.377-0.203	< 0.001
Malawi	4	0.399	2010	-0.289	-0.386-0.192	< 0.001
Mali	3	0.126	2012	0.045	-0.138-0.227	0.631
Mozambique	3	0.059	2011	0.084	-0.038-0.206	0.179
Nigeria	5	0.180	2013	0.343	0.211-0.475	< 0.001
Kenya	3	0.067	2008	-0.009	-0.096-0.078	0.840
Senegal	4	0.059	2014	-0.313	-0.488-0.138	< 0.001
Tanzania	4	0.048	2010	-0.218	-0.287-0.149	< 0.001
Uganda	4	0.047	2011	-0.079	-0.158-0.001	0.047
Zimbabwe	5	0.033	2014	-0.247	-0.311-0.183	< 0.001
Underweight among children						
Burkina Faso	4	0.257	2010	-0.445	-0.631-0.260	< 0.001
Cameroon	3	0.146	2011	-0.092	-0.361-0.178	0.505
Ivory Coast	3	0.149	2011	-0.240	-0.474-0.007	0.043
Ghana	6	0.110	2014	-0.525	-0.649-0.400	< 0.001
Malawi	4	0.128	2010	-0.767	-0.930-0.604	< 0.001
Mali	3	0.255	2012	-0.347	-0.565-0.129	0.002
Mozambique	3	0.149	2011	-0.593	-0.801-0.385	< 0.001
Nigeria	5	0.287	2013	0.589	0.390-0.789	< 0.001
Kenya	3	0.161	2008	-0.212	-0.367-0.057	0.007
Senegal	4	0.126	2014	-0.152	-0.425-0.121	0.274
Tanzania	4	0.158	2010	-0.723	-0.858-0.589	< 0.001
Uganda	4	0.138	2011	-0.437	-0.572-0.301	< 0.001
Zimbabwe	5	0.112	2014	0.002	-0.088-0.093	0.958
Birth weight						
Burkina Faso	4	0.139	2010	-0.138	-0.317-0.042	0.133
Cameroon	3	0.076	2011	-0.179	-0.362-0.004	0.055
Ivory Coast	3	0.142	2011	-0.122	-0.322-0.079	0.234
Ghana	6	0.095	2014	0.096	-0.057-0.250	0.220
Malawi	4	0.123	2010	0.135	0.012-0.258	0.032
Mali	3	0.155	2012	0.031	-0.228-0.291	0.813
Mozambique	3	0.141	2011	0.126	-0.101-0.353	0.277
Nigeria	5	0.081	2013	-0.071	-0.295-0.153	0.532
Kenya	3	0.056	2008	-0.194	-0.312-0.0753	0.001
Senegal	5	0.132	2014	0.173	0.042-0.305	0.010
Tanzania	4	0.069	2010	-0.241	-0.357-0.124	< 0.001
Uganda	4	0.102	2011	-0.047	-0.170-0.076	0.452
Zimbabwe	5	0.087	2014	-0.067	-0.179-0.045	0.239

N = total number of surveys; pp/yr = annual percentage point change in the indicator; CI = confidence interval. Prev.= prevalence at the end of the series (most recent year).

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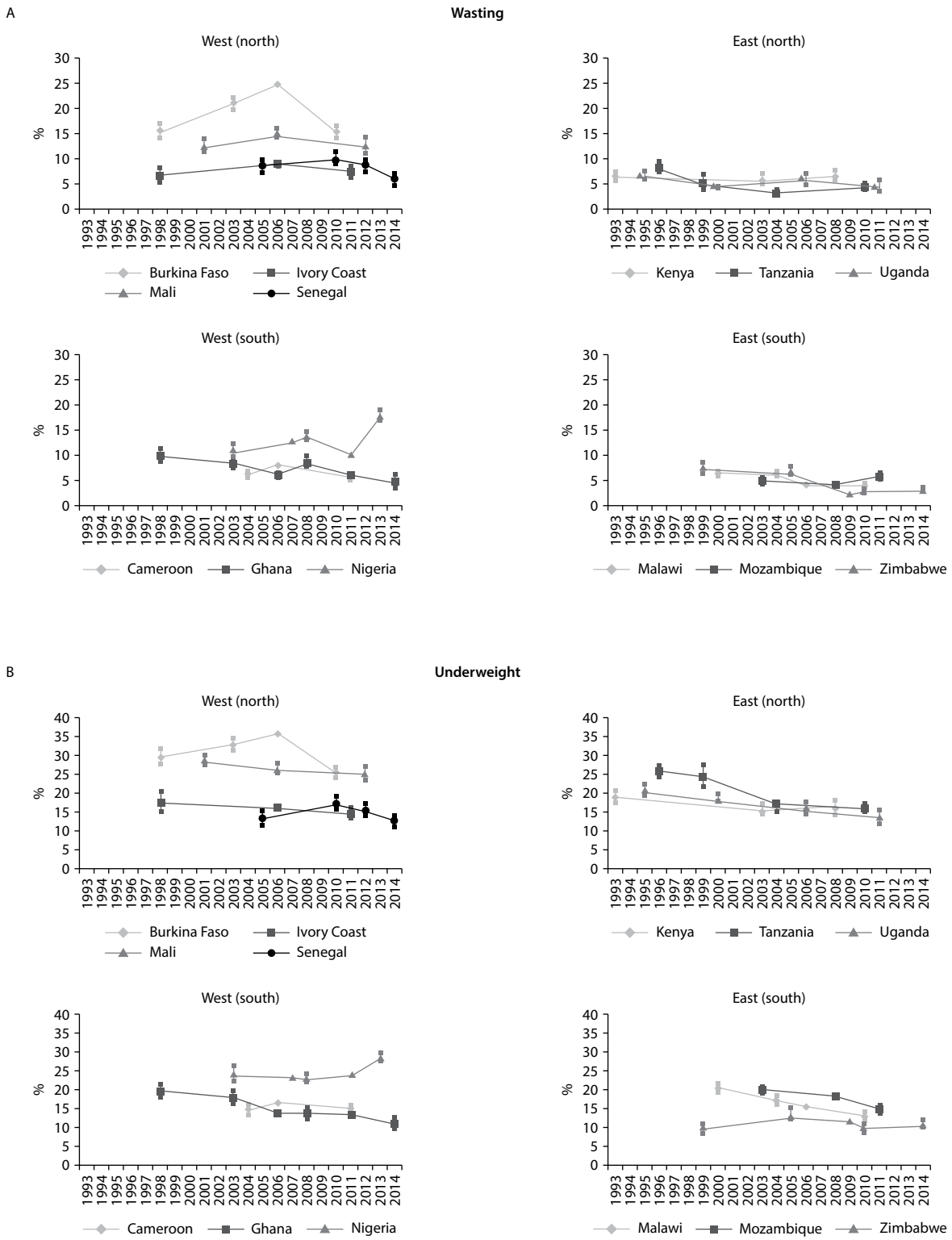

Sources: demographic and health surveys (DHS) (http://www.measuredhs.com/aboutsurveys/dhs/star.cfm) and multiple indicator cluster surveys (MICS) (http://www.childinfo.org/).

Figure 2. Panel A. Trends in wasting among children under five years of age in 13 sub-Saharan African countries. Panel B. Trends in underweight among children under five years of age in 13 sub-Saharan African countries. Panel C. Trends in low birth weight among children under five years of age in 13 sub-Saharan African countries.

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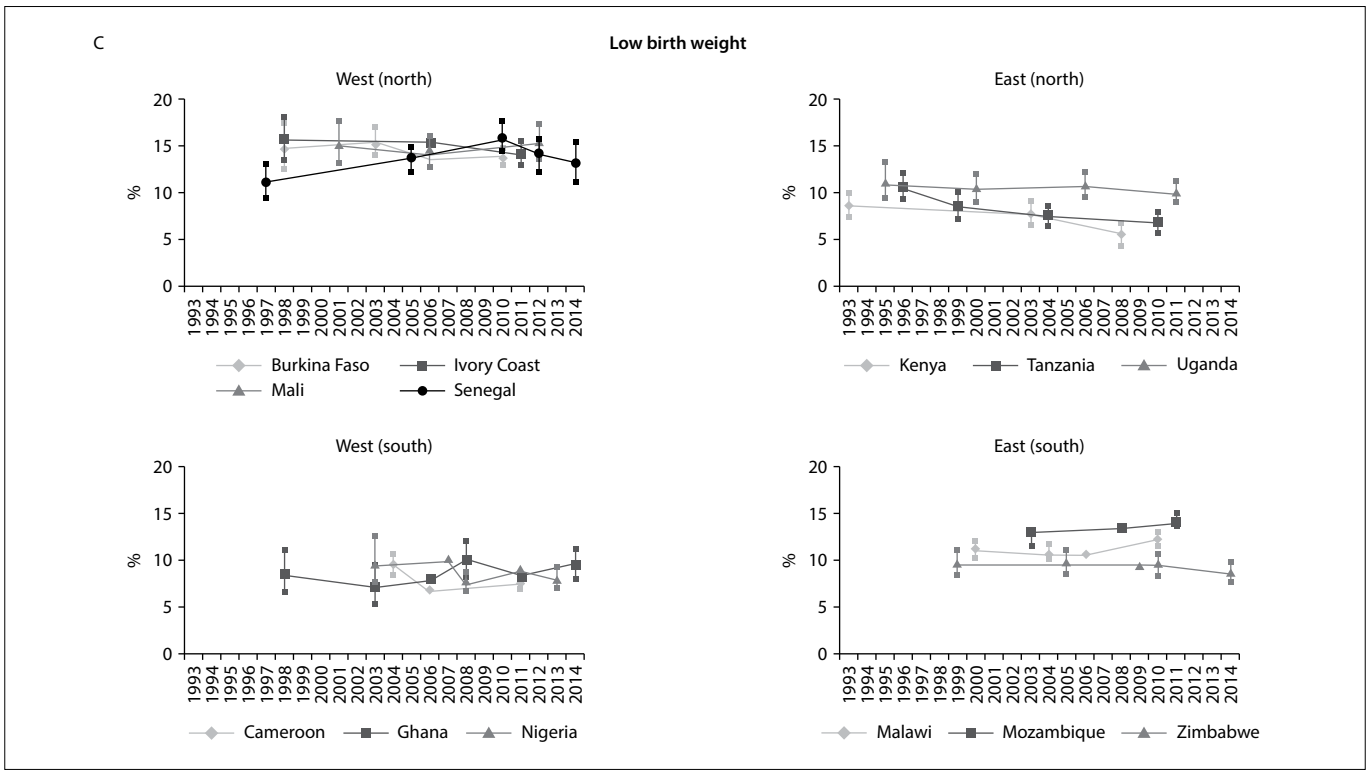

Figure 2. Continuation.

women to maintain a healthy weight before and during pregnancy. They also highlight the importance of avoidance of later nutritional excess among sub-Saharans who previously suffered from undernutrition during fetal life and early infancy.

In sum, these findings suggest that the time has come for public health officials in sub-Saharan African countries to implement policies for controlling obesity that include attention to women of childbearing age and young children. In global terms, overweight and obesity have already replaced undernutrition and infectious diseases as the major cause of health-related problems in the 21st century.[31,32] There is little reason to believe that sub-Saharan Africa will not follow the pattern already established in most of the world's other regions. In sub-Saharan Africa, women of childbearing age are an important target population for efforts to improve the nutritional status of future generations, since they are the key to better nutrition during fetal life and, through breastfeeding, in early childhood. For children under five years of age, growth monitoring and immunization campaigns can boost efforts to maintain balanced nutrition. Development of nutritional programs to provide better information to families about healthy eating and the importance of preventing noncommunicable diseases is also a key necessity.[30,33] Policies to combat economic inequality and poverty, which are striking features of present-day Africa; to combat obesogenic social changes, such as increasing advertising and availability of unhealthy foods and snacks to children; to encourage physical activity; to promote family farming; to support gender equality; and to improve access to health care and education[34] will also be beneficial in this effort. The complex challenge for many transitioning African countries will be to simultaneously address childhood undernutrition, on the one hand, and excess weight, on the other.[34]

Table 3. Trends in the nutritional indicators studied, in a summary analysis involving all 13 countries over the period 1993-2014

Variable	N	pp/yr	95% CI	P-value
Obesity, women 15-49 years	45	0.279	0.211-0.347	< 0.001
Overweight	51	0.101	-0.236-0.033	0.138
Stunting	51	-0.517	-0.685-0.350	< 0.001
Wasting	51	-0.107	-0.232-0.017	0.092
Underweight	51	-0.324	-0.462-0.186	< 0.001
Low birth weight	51	-0.032	-0.0908-0.028	0.296

N = total number of surveys; pp/yr = annual percentage point change in the indicator; CI = confidence interval.

Some limitations of our study merit comment. The group of 13 countries analyzed is not fully representative of sub-Saharan Africa, since the countries were selected based on survey availability. Therefore, caution is needed when generalizing the results. However, it is noteworthy that many of the sub-Saharan African countries with the highest obesity rates (those located in the south)

were not included in our sample because they lacked a minimum number of surveys. Another limitation was our use of the body mass index to estimate cutoffs for overweight, given the widespread presence of stunting, because the progression to future overweight and obesity among children currently presenting stunting (a situation involving a large proportion of the children under five years of age in these countries) is less well understood. Nevertheless, we can highlight that one strength of our study was our use of available, high-quality data to summarize the current picture, thereby providing useful information for the public healthcare services of the countries involved.

CONCLUSION

Our results demonstrate the presence of an epidemiologically significant upward trend in the prevalence of obesity among women of childbearing age in most of the sub-Saharan African countries included in this study. This change has been accompanied by heterogeneous, but on average relatively stable presence of overweight among children under five years of age and by significant reductions in the prevalence of chronic undernutrition. Given the context of the current obesity pandemic and the ongoing shift of disease burden to noncommunicable diseases in these countries, policymakers should place greater focus on interventions aiming to improve the nutritional status of women of childbearing age and children during the first years of life in sub-Saharan Africa, not only to eradicate states of nutritional deficiency but also to prevent states of nutritional excess.

REFERENCES

1. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/. Accessed in 2018 (Jan 5).
2. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: WHO; 2014. Available from: http://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed in 2018 (Jan 5).
3. United Nations. General Assembly. Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases. Geneva: UN; 2012. Available from: http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf?ua=1. Accessed in 2018 (Jan 5).
4. Duki Y, Naidoo DP. Relationship of Body Anthropometry with Cardiovascular Risk Factors in a Random Community Sample: The Phoenix Lifestyle Project. Metab Syndr Relat Disord. 2016;14(2):102-7. PMID: 26808094; doi: 10.1089/met.2015.0072.
5. Popkin BM. Synthesis and implications: China's nutrition transition in the context of changes across other low- and middle-income countries. Obes Rev. 2014;15 Suppl 1:60-7. PMID: 24341759; doi: 10.1111/obr.12120.
6. World Health Organization. The WHO Child Growth Standards. Geneva; WHO; 2010. Available from: http://www.who.int/childgrowth/standards/en/. Accessed in 2017 (Aug 28).
7. United Nations News Service Section. Governments must act to reverse alarming rise in childhood obesity. UN News Service Section. 2016. Available from: http://www.un.org/apps/news/story.asp?NewsID=53084#.WYJafYjyuM9. Accessed in 2017 (Aug 28).
8. International Food Policy Research Institute. From Promise to Impact: Ending Malnutrition by 2030. Washington: IFPRI; 2016. Available from: http://www.ifpri.org/publication/global-nutrition-report-2016-promise-impact-ending-malnutrition-2030. Accessed in 2018 (Jan 5).
9. United States Agency International Development. Available Datasets. The DHS Program. 2017. Available from: http://dhsprogram.com/data/available-datasets.cfm. Accessed in 2017 (Aug 28).
10. United Nations Children's Fund. The state of the world's children 2016: a fair chance for every child. New York: UNICEF; 2016. Available from: https://www.unicef.org/publications/files/UNICEF_SOWC_2016.pdf. Accessed in 2018 (Jan 5).
11. United States Agency International Development. Survey Organization Manual for Demographic and Health Surveys. MEASURE DHS. Calverton: ICF International; 2012. Available from: https://dhsprogram.com/pubs/pdf/DHSM10/DHS6_Survey_Org_Manual_7Dec2012_DHSM10.pdf. Accessed in 2018 (Jan 5).
12. World Health Organization. WHO Global Database on Child Growth and Malnutrition. WHO; 2017. Available from: http://www.who.int/nutgrowthdb/en/. Accessed in 2017 (Aug 2).
13. World Health Organization. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: WHO; 2006. ISBN 92 4 154693 X.
14. Restrepo-Méndez MC, Barros AJ, Requejo J, et al. Progress in reducing inequalities in reproductive, maternal, newborn, and child health in Latin America and the Caribbean: an unfinished agenda. Rev Panam Salud Publica. 2015;38(1):9-16. PMID: 26506316.
15. Nutrition Landscape Information System (NLIS). Country Profile Indicators: Interpretation Guide. Geneva: WHO; 2010. ISBN: 978 92 4 159995 5.
16. Jaacks LM, Slining MM, Popkin BM. Recent underweight and overweight trends by rural-urban residence among women in low- and middle-income countries. J Nutr. 2015;145(2):352-7. PMID: 25644358; doi: 10.3945/jn.114.203562.
17. World Health Organization. Controlling the global obesity epidemic. Geneva: WHO; 2007. Available from: http://www.who.int/nutrition/topics/obesity/en/. Accessed in 2017 (Aug 28).
18. Jones-Smith JC, Gordon-Larsen P, Siddiqi A, Popkin BM. Is the burden of overweight shifting to the poor across the globe? Time trends among women in 39 low- and middle-income countries (1991-2008). Int J Obes (Lond). 2012;36(8):1114-20. PMID: 21912397; doi: 10.1038/ijo.2011.179.

19. Razak F, Corsi DJ, Subramanian SV. Change in the body mass index distribution for women: analysis of surveys from 37 low- and middle-income countries. PLoS Med. 2013;10(1):e1001367. PMID: 23335861; doi: 10.1371/journal.pmed.1001367.
20. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81. PMID: 24880830; doi: 10.1016/S0140-6736(14)60460-8.
21. Adair LS, Fall CH, Osmond C, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. Lancet. 2013;382(9891):525-34. PMID: 23541370; doi: 10.1016/S0140-6736(13)60103-8.
22. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382(9890):427-51. PMID: 23746772; doi: 10.1016/S0140-6736(13)60937-X.
23. Olofin I, McDonald CM, Ezzati M, et al. Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies. PLoS One. 2013;8(5):e64636. PMID: 23734210; doi: 10.1371/journal.pone.0064636.
24. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes Care. 2008;31(2):340-6. PMID: 18000174; doi: 10.2337/dc07-1596.
25. Liu P, Xu L, Wang Y, et al. Association between perinatal outcomes and maternal pre-pregnancy body mass index. Obes Rev. 2016;17(11):1091-102. PMID: 27536879; doi: 10.1111/obr.12455.
26. Farrar D, Simmonds M, Bryant M, et al. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. BMJ. 2016;354:i4694. PMID: 27624087; doi: 10.1136/bmj.i4694.
27. Fraser A, Lawlor DA. Long-term health outcomes in offspring born to women with diabetes in pregnancy. Curr Diab Rep. 2014;14(5):489. PMID: 24664798; doi: 10.1007/s11892-014-0489-x.
28. Rockenbach G, Luft VC, Mueller NT, et al. Sex-specific associations of birth weight with measures of adiposity in mid-to-late adulthood: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Int J Obes (Lond). 2016;40(8):1286-91. PMID: 27121250; doi: 10.1038/ijo.2016.76.
29. Hult M, Tornhammar P, Ueda P, et al. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PloS One. 2010;5(10):e13582. PMID: 21042579; doi: 10.1371/journal.pone.0013582.
30. Chavey A, Ah Kioon M-D, Bailbé D, Movassat J, Portha B. Maternal diabetes, programming of beta-cell disorders and intergenerational risk of type 2 diabetes. Diabetes Metab. 2014;40(5):323-30. PMID: 24948417; doi: 10.1016/j.diabet.2014.02.003.
31. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1659-724. PMID: 27733284; doi: 10.1016/S0140-6736(16)31679-8.
32. United Nations Children's Fund, World Health Organization, World Bank Group. Levels and trends in child malnutrition: key findings of the 2015 edition. New York: UNICEF; 2015. Available from: http://www.who.int/nutgrowthdb/jme_brochure2015.pdf. Accessed in 2018 (Jan 5).
33. Hawkes C, Smith TG, Jewell J, et al. Smart food policies for obesity prevention. Lancet. 2015;385(9985):2410-21. PMID: 25703109; doi: 10.1016/S0140-6736(14)61745-1.
34. Norris SA, Wrottesley S, Mohamed RS, Micklesfield LK. Africa in transition: growth trends in children and implications for nutrition. Ann Nutr Metab. 2014;64 Suppl 2:8-13. PMID: 25341869; doi: 10.1159/000365122.

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Comparison of health-related quality of life between patients with different metatarsalgia types and matched healthy controls: a cross-sectional analysis

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KEY WORDS:
Foot deformities.
Foot diseases.
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Quality of life.

ABSTRACT

BACKGROUND: Metatarsalgia can be considered to be a common complaint in clinical practice. The aim of this study was to compare quality of life (QoL) between participants with different metatarsalgia types and matched-paired healthy controls.

DESIGN AND SETTING: A cross-sectional analysis on a sample of 124 participants of median age ± interquartile range of 55 ± 22 years was carried out in the University Clinic of Podiatric Medicine and Surgery, Ferrol, Spain. They presented primary (n = 31), secondary (n = 31) or iatrogenic (n = 31) metatarsalgia, or were matched-paired healthy controls (n = 31).

METHODS: Self-reported domain scores were obtained using the Foot Health Status Questionnaire (FHSQ) and were compared between the participants with metatarsalgia and between these and the healthy controls.

RESULTS: Statistically significant differences were shown in all FHSQ domains ($P \leq 0.001$). Post-hoc analyses showed statistically significant differences ($P < 0.05$) between the metatarsalgia types in relation to the matched healthy control group, such that the participants with metatarsalgia presented impaired foot-specific and general health-related QoL (lower FHSQ scores).

CONCLUSION: This study demonstrated that presence of metatarsalgia had a negative impact on foot health-related QoL. Foot-specific health and general health were poorer among patients with metatarsalgia, especially among those with secondary and iatrogenic metatarsalgia, in comparison with matched healthy controls.

INTRODUCTION

One of the most common forms of soreness of the feet is metatarsalgia. It is defined as acute or chronic pain in one or more metatarsophalangeal joints.[1-6] This condition may be characterized as one of the most frequent symptoms in subjects with foot problems. Its prevalence in the general population is 10% and this may increase up to 50%-95% in older adults. Metatarsalgia can be considered to be the most frequent cause of foot pain in middle-aged women, accounting for approximately 85% of foot pain in that population.[7-9] Up to 80% of the population may develop some kind of soreness in the metatarsal region over their lifetimes.[10] Prevalence of 10% was reported in one population, with predominance in females.[11] Foot soreness may affect approximately one-third of community-dwelling older adults.[12] In a prospective cohort study among adults aged 50 years and over, the incidence of disabling foot soreness was found to reach 8.1% after a three-year follow-up and it increased with increasing age.[13]

Forefoot pain or metatarsalgia is a frequent symptom secondary to various conditions. Thus, knowledge of anatomical pathology in this area needs to be improved in order to achieve better differentiation regarding these processes.[9] Metatarsalgia may not be limited only to pain in the foot sole: it may also be dorsal, lateral or medial, or be in a combination of these three regions. The local soreness may be accompanied by hyperkeratosis, helomas, claw or hammer toe deformities or subluxation of the metatarsophalangeal joints, or may be attributed to iatrogenic surgery.[2,14] Mechanical metatarsalgia produces pain in the forefoot accompanied by plantar hyperkeratosis because of the key role of the metatarsal heads.[15]

Regarding the pathophysiology and treatment of metatarsalgia, this condition should be understood as secondary to anatomical and biomechanical alterations.[15] Its origins may be varied, and some causes (e.g. rheumatoid arthritis) may be very complex. A wide degree of variability regarding the possible causal factors of metatarsalgia has been reported. Nevertheless, gait and posture biomechanics, along with foot and ankle deformities, may be considered to be key factors.[16,17] Metatarsalgia may be secondary to damage (mechanical or of other origin) to anatomical structures surrounding the joint (capsule, ligaments, vessels, bone, cartilage, nerves, tendons, bursa, subcutaneous tissue or skin).[1-6] Metatarsalgia may be secondary to three groups of etiological factors: general diseases (i.e. inflammatory, metabolic, neurological or congenital conditions); anatomical and functional alterations (i.e. mechanical, static or propulsion factors); and iatrogenic or traumatic factors.[18] Local bone and joint deformities, metabolic conditions, neuropathies and autoimmune conditions seem to be associated with metatarsalgia. However, the most significant associations are probably bipedal biomechanical alterations, inappropriate footwear use, repeated trauma and non-walking habits.[9]

This major health problem seems to be more frequent among females (85% of the population affected). Gout or rheumatoid arthritis may generate metatarsalgia, and this involves the distal metatarsophalangeal and interphalangeal joints.[9] The soreness may be located in the metatarsal region of the forefoot and may increase through plantar pressure during standing and walking. Biomechanical alterations secondary to use of inappropriate footwear or deformities (e.g. hallux rigidus) may produce metatarsalgia in which the pain seems to be transmitted laterally because of load-shifting from the hallux to the smaller toes.[19] The point at which metatarsalgia is generated is a key factor in understanding its cause.

Various classifications for metatarsalgia have been described in the literature.[2,20] Primary metatarsalgia consists of first-ray hypermobility or metatarsal plantar flexion, prominent metatarsal heads (i.e. due to arthritis, tumors, infection or congenital or hereditary conditions), metatarsal length discrepancy and equinus condition (i.e. high-arched feet with contracture of the triceps surae muscles). Secondary metatarsalgia consists of metabolic disorders (e.g. gout), systemic conditions (e.g. rheumatoid arthritis or metatarsal phalangeal joints), trauma, neurological conditions (e.g. Morton's neuroma or tarsal tunnel syndrome) and Freiberg disease. Iatrogenic metatarsalgia results from failure of surgical treatment for hallux abducto valgus consisting of arthrodesis of the first metatarsophalangeal joint, metatarsal osteotomy and shortened second ray.

A risk of falls and a decrease in physical activity may appear secondarily to foot pain, and these may promote a reduction in the quality of life (QoL).[21,22] Reduction in physical activity has been reported to increase mortality.[23] Regular daily walking may be healthy and may lead to a longer life.[24] In addition, use of inadequate footwear may be very frequent among older adults, and this is highly related to forefoot deformities such as hallux valgus or hammer or claw toes.[25] An increase in plantar pressure under the metatarsal heads may occur secondarily to these deformities, thus generating metatarsalgia.[26] The risk of falls was shown to be higher among adults with foot soreness or toe deformities.[27,28] Therefore, early comprehensive podiatric intervention should be recommended in order to prevent falls among older adults with disabling foot soreness.[29]

We hypothesized that increasing degrees of severity of metatarsalgia will decrease the QoL of patients who suffer from this condition.

OBJECTIVE

The aim of this study was to compare the impacts of various degrees of metatarsalgia on quality of life relating to foot health, in a sample of patients with metatarsalgia and in healthy control subjects.

METHODS

Design and sample

A cross-sectional analysis was carried out from September 2015 to April 2016 at a clinic of podiatric medicine and surgery in the city of Ferrol, in the province of A Coruña, Spain, to study quality of life among subjects with metatarsalgia. All consecutive patients with foot pain who were seen at this clinic during this period were invited to participate in this study. Non-probabilistic convenience sampling was used in order to recruit participants, and the ages of these subjects ranged from 20 to 87 years. All subjects were required to be able to walk independently without an assistive device.

The following subjects were excluded: people with immune-comprised treatment, neurological conditions, lack of autonomy in daily activities or cognitive impairment (as determined using the Short Portable Mental Status Questionnaire, with scores < 7); and participants who declined to sign the consent form.

Sample size calculation

The sample size calculation was carried out by means of the one-way analysis of variance F test (fixed effects-omnibus ANOVA) using the G*Power 3.1.9.2 software. It was based on the general health domain of the FHSQ[30] of a pilot study (n = 60 participants) with four groups, taking the mean: 15 patients with primary metatarsalgia (72.00 points), 15 patients with secondary metatarsalgia (57.33 points), 15 patients with iatrogenic metatarsalgia (59.33 points) and 15 matched-paired healthy controls (79.33 points). The total standard deviation (SD) within each

group was 25.86 points. An effect size of 0.35, an α error probability of 0.05 and a power (1-β error probability) of 0.90 were used for the sample size calculation. Therefore, the total size of the sample was determined to be a minimum of 120 participants, i.e. 30 for each group. In the end, a total sample of 124 participants, i.e. 21 per group, was included in this study.

Procedures

A single podiatrist researcher carried out all measurements. Height and weight were measured and body mass index (BMI) was calculated. The degree of metatarsalgia was established through a foot examination that was conducted in accordance with the classification proposed by Espinosa et al. In this, three kinds of metatarsalgia (primary, secondary and iatrogenic) are defined by using the mini-Lachman test to evaluate the integrity of the toe plantar plate at the metatarsophalangeal joint.[20]

Primary metatarsalgia may be secondary to mild translation, signifying that the plantar plate is intact. Secondary metatarsalgia may appear when the plantar plate is torn or attenuated secondary to reducible dislocation of the joint that may occur when mild force is exerted.[31] Iatrogenic metatarsalgia may be diagnosed as an occurrence secondary to the past medical history. Patients without metatarsalgia and showing integrity of the toe plantar plate at the metatarsophalangeal joint, without signs or symptoms related with this condition, were included as controls, following the classification proposed by Espinosa et al.[20] These controls were recruited if they had sociodemographic characteristics that were similar to those of the case groups.

The study subjects self-reported their conditions using the Foot Health Status Questionnaire (FHSQ). This questionnaire regarding health-related QoL is intended specifically for the foot and has been recognized as a validated tool that has been translated into Spanish.[29,32,33] Both foot-specific and general health-related QoL have been evaluated using the FHSQ (version 1.03),[33] which consists of three main sections.

Section 1 of FHSQ consists of 13 items reflecting four foot health-related domains: foot pain; foot function; footwear; and general foot health. This section has shown a high degree of content, criterion and construct validity (Cronbach α = 0.89-0.95) and high retest reliability (intraclass correlation coefficient = 0.74-0.92)[22] and has been determined to be the most appropriate measurement of health-related QoL for patients with chronic plantar heel pain.[34] Each domain has a specific number of questions, of which four refer to pain, four to function, three to footwear and two to general foot health. The pain and function evaluations are based on physical phenomena. Footwear assessment includes practical issues relating to shoe availability and comfort, and the perception of general foot health is based on patients' self-assessment of the state of their feet. Several possible answers are presented on a Likert-type ordinal scale. The scale descriptors vary for each domain, and the participant determines only one response as the most appropriate. The questionnaire does not provide any overall score but, rather, it generates a score for each domain. The responses are analyzed using computer software (FHSQ, version 1.03) and the scores range from 0 to 100. A score of 0 represents the worst health-related QoL state for the foot and 100 indicates the best possible health-related QoL state for the foot. In addition, the software provides graphical illustrations of the outcomes.

Section 2 includes items that reflect four general health-related domains: general health, physical activity, social capacity and vigor. The domains and items in this section are largely adapted from the short form-36 (SF-36) survey,[34] which has been validated (the Cronbach α ranges from 0.89 to 0.95), with high retest reliability (the intraclass correlation coefficient ranges from 0.74 to 0.92) for the Spanish version.[29,35]

Section 3 collects data on socioeconomic status, comorbidities, service utilization, satisfaction and medical records.

Ethical considerations

The Research Ethics Committee of the University of Coruña, Spain, approved this study, under registration number C.E.I. 01/2015, with application date March 6, 2015. All the patients participated voluntarily and gave their consent in written form. The ethical standards for human research and the Declaration of Helsinki (World Medical Association) and rules from other appropriate national/institutional organizations were respected.

Statistical analysis

Descriptive analysis on the variables included in the study and comparisons between patients with primary, secondary and iatrogenic metatarsalgia and between these and matched healthy controls were made in accordance with the sample size calculation. The Shapiro-Wilk test was performed to determine the distribution of the variables. Categorical data appeared as frequencies and percentages and between-group comparisons were analyzed using the chi-square (χ^2) test. Parametric quantitative data were analyzed using means and standard deviations (SD) and the range (maximum and minimum values). Between-group comparisons were analyzed using one-way analysis of variance (ANOVA). Non-parametric quantitative data, including medians, interquartile ranges (IR) and ranges (maximum and minimum values), along with between-group comparisons, were analyzed using the Kruskal-Wallis test. Because all FHSQ domains presented nonparametric data, the Kruskal-Wallis test was complemented by means of the Wilcoxon test, with adjustment using Bonferroni's correction in order to determine any post-hoc differences. The IBM SPSS 22.0 statistics package was used for the analyses on the data. FHSQ version 1.03 was used to obtain QoL

scores relating to foot health. In all the analyses, $P < 0.05$ (with a 95% confidence interval) was considered statistically significant, unless otherwise stated.

RESULTS

A total sample of 124 people between 20 and 87 years of age completed the study. The sample included 76 women (61.3%) and 48 men (38.7%). **Table 1** shows that the patients' clinical and sociodemographic characteristics were homogenous, given that there were no statistically significant differences ($P > 0.05$).

In the control group, there were 31 study participants. In the metatarsalgia group, there were 93 study participants, with 31 participants in each group (primary, secondary and iatrogenic metatarsalgia). The results from comparisons between the FHSQ scores according to the degree of metatarsalgia and between these groups and matched controls are shown in **Table 2**. Section One of the FHSQ showed statistically significant differences ($P < 0.001$) for the four foot-specific domains:

1. pain;
2. function;
3. health; and
4. footwear.

Post-hoc analyses showed statistically significant differences ($P < 0.05$) between all metatarsalgia types with regard to the matched healthy control group, for foot pain and footwear; and also between the secondary and iatrogenic metatarsalgia types with regard to the matched healthy control group for foot function and general foot health, thus showing impaired foot-specific health-related quality of life (lower FHSQ scores).

Section Two of the FHSQ provided statistically significant differences ($P \leq 0.001$) for the four overall wellbeing domains:

1. overall health;
2. physical function;
3. social capacity; and
4. vigor.

Post-hoc analyses showed statistically significant differences ($P < 0.05$) between the secondary and iatrogenic metatarsalgia types with regard to the matched healthy control group, thus showing impaired general health-related quality of life (lower FHSQ scores).

The rest of the comparisons did not show any statistically significant differences ($P > 0.05$).

Table 1. Sociodemographic characteristics of patients with primary, secondary and iatrogenic metatarsalgia and matched healthy controls

Sociodemographic characteristics		Control group n = 31	Primary metatarsalgia n = 31	Secondary metatarsalgia n = 31	Iatrogenic metatarsalgia n = 31	P-value
Age (years)		41.00 ± 30.00 (20-80)	58.00 ± 15.00 (30-65)	59.00 ± 14.00 (20-82)	55.00 ± 12.00 (25-87)	0.051†
Weight (kg)		72.00 ± 12.00 (56-100)	72.00 ± 17.00 (50-110)	74.00 ± 18.00 (50-110)	72.00 ± 11.00 (58-100)	0.656†
Height (cm)		169.71 ± 6.62 (155-180)	166.97 ± 7.96 (151-182)	168.29 ± 8.89 (150-183)	166.35 ± 7.51 (155-190)	0.338*
BMI (kg/cm^2)		24.70 ± 3.20 (20-80)	25.00 ± 5.70 (20-44)	25.70 ± 6.60 (19-39)	24.70 ± 3.20 (19-41)	0.439†
Sex	Male	14 (11.3%)	9 (7.3%)	14 (11.3%)	11 (8.9%)	0.485‡
	Female	17 (13.7%)	22 (17.7%)	17 (13.7%)	20 (16.1%)	
Professional activity	Student	2 (1.6%)	0 (0%)	1 (0.8%)	1 (0.8%)	0.276‡
	Freelance	4 (3.2%)	1 (0.8%)	2 (1.6%)	1 (0.8%)	
	Employed	14 (11.3%)	12 (9.7%)	6 (4.8%)	12 (9.7%)	
	Unemployed	3 (2.4%)	11 (8.9%)	11 (8.9%)	9 (7.3%)	
	Retired	8 (6.5%)	7 (5.6%)	11 (8.9)	8 (6.5%)	
Study level	I. primary	5 (4%)	8 (6.5%)	6 (6.5%)	6 (4.8%)	0.912‡
	C. primary	6 (4.8%)	7 (5.6%)	8 (6.5%)	7 (5.6%)	
	Secondary	8 (6.5%)	11 (8.9%)	8 (6.5%)	9 (7.3%)	
	Degree	9 (7.3%)	4 (3.2%)	5 (4%)	7 (5.6%)	
	H. Degree	3 (2.4%)	1 (0.8%)	4 (3.2%)	2 (1.6%)	
Civil status	Single	3 (2.4%)	2 (1.6%)	2 (1.6%)	1 (0.8%)	0.089‡
	Divorced	2 (1.6%)	3 (4.4%)	1 (0.8%)	4 (5.2%)	
	Widowed	2 (1.6%)	2 (1.6%)	5 (4%)	7 (5.6%)	
	Couple	4 (3.2%)	1 (0.8%)	1 (0.8%)	7 (5.6%)	
	Married	20 (16.1%)	23 (18.5%)	22 (17.7%)	12 (9.7%)	

BMI = body mass index; C = complete; I = incomplete; H = higher.

*Mean ± standard deviation (SD), range (min–max) and one-way analysis of variance (ANOVA) were used.

†Median ± interquartile range (IR), range (min–max) and Kruskal-Wallis test were used.

‡Frequency, percentage (%) and chi-square test (χ^2) were used.

Table 2. Comparisons of FHSQ scores between patients with primary, secondary and iatrogenic metatarsalgia and matched healthy controls

	Control (C) group Median (IR) n =31	Primary (P) metatarsalgia group Median (IR) n = 31	Secondary (S) metatarsalgia group Median (IR) n = 31	Iatrogenic (I) metatarsalgia group Median (IR) n = 31	Kruskal-Wallis P-value	Paired group comparison Wilcoxon P-value
Foot pain	90.62 ± 21.88 (29.38-100)	72.50 ± 39.38 (10.63-100)	43.75 ± 47.50 (0-100)	54.37 ± 56.25 (0-100)	**< 0.001**	**1. P vs C**** **2. S vs C**† **3. I vs C**† 4. S vs P 5. I vs P 6. I vs S
Foot function	100.0 ± 12.50 (25-100)	81.25 ± 43.75 (6.25-100)	56.25 ± 50.00 (0-100)	68.75 ± 56.25 (0-100)	**< 0.001**	1. P vs C **2. S vs C**† **3. I vs C**** 4. S vs P 5. I vs P 6. I vs S
Footwear	75.00 ± 50.00 (25-100)	50.00 ± 50.00 (0-100)	50.00 ± 33.33 (0-100)	50.00 ± 41.67 (0-100)	**< 0.001**	**1. P vs C*** **2. S vs C**** **3. I vs C**** 4. S vs P 5. I vs P 6. I vs S
General foot health	79.67 ± 20.00 (25-100)	60.00 ± 60.00 (12.50-100)	42.50 ± 35.00 (0-100)	85.00 ± 20.00 (25-100)	**< 0.001**	**1. P vs C*** **2. S vs C**† **3. I vs C**** 4. S vs P 5. I vs P 6. I vs S
General health	100.0 ± 30.00 (40-100)	80.00 ± 40.00 (10-100)	50.00 ± 40.00 (0-100)	70.00 ± 40.00 (0-100)	**< 0.001**	1. P vs C **2. S vs C**† **3. I vs C**† 4. S vs P 5. I vs P 6. I vs S
Physical activity	100.0 ± 11.11 (38.89-100)	88.88 ± 33.33 (38.89-100)	66.66 ± 27.78 (11.11-100)	83.33 ± 33.33 (5.56-100)	**0.001**	1. P vs C **2. S vs C**† **3. I vs C*** 4. S vs P 5. I vs P 6. I vs S
Social capacity	100.0 ± 00.00 (50-100)	87.50 ± 25.00 (37.50-100)	75.00 ± 50.00 (25-100)	87.50 ± 50.00 (12.50-100)	**0.001**	1. P vs C **2. S vs C**** **3. I vs C*** 4. S vs P 5. I vs P 6. I vs S
Vigor	75.00 ± 25.00 (50-100)	62.50 ± 31.25 (12.50-100)	50.00 ± 18.75 (25-100)	56.25 ± 18.75 (25-100)	**< 0.001**	1. P vs C **2. S vs C**† **3. I vs C*** 4. S vs P 5. I vs P 6. I vs S

FHSQ = Foot Health Status Questionnaire Survey; IR = interquartile range; vs = versus. *Statistically significant at P-value < 0.05 adjusted using Bonferroni's correction. **Statistically significant at P-value < 0.01 adjusted using Bonferroni's correction. †Statistically significant at P-value < 0.001 adjusted using Bonferroni's correction.

DISCUSSION

The main aim of this study was to assess the impact of different degrees of metatarsalgia on health-related QoL in a sample of patients with such conditions, compared with a healthy control group. Proper foot health may be essential, and 75% of adults complain of foot soreness in association with significant foot problems, with evidence of arthritic changes on X-rays.[36] Falls may be common among older adults, with consequences such as major threats to their health, along with higher costs and economic burdens for healthcare services. Foot problems have been identified as risk factors for falls, and painful feet may be associated with increased risk of falls and decreased mobility and QoL.[37] Despite this, the role of physical rehabilitation in fall prevention programs may be negligible,[38] and supporting evidence for this practice in relation to metatarsalgia is scarce. Menz and Lord reported that older adults with foot pain and plantar hyperkeratosis showed worse balance and functional ability than those with other foot problems and no soreness.[39]

Numerous studies have addressed the issue of metatarsalgia, regarding its clinical features and treatment.[40-42] Nevertheless, there has been no research evaluating the impact of metatarsalgia on patients' QoL. Gines et al. assessed QoL among patients with hallux valgus and, additionally, compared these findings with results from patients who suffered from hallux valgus and metatarsalgia in order to state which of these two groups showed worse QoL.[42] Because of the lack of epidemiological data regarding metatarsalgia, it is difficult to estimate the influence that this condition has on foot health-related QoL among participants with different kinds of metatarsalgia. The results from the present study confirmed that subjects with metatarsalgia presented lower scores in all dimensions relating to footwear, general foot health, foot pain, foot function, vigor, physical activity, social capacity and general health, in comparison with the healthy control group. From a physical rehabilitation point of view, it is important to understand the results from this study in order to develop healthcare programs for promoting foot health according to the degree of these patients' metatarsalgia.

We did not find any reports in the literature evaluating the impact of metatarsalgia on QoL. It would be beneficial to establish the extent to which metatarsalgia may affect general health and foot health. This would be useful prior to formulating a physical rehabilitation program, in order to determine the effectiveness of physical rehabilitation programs and the benefits that are obtained secondarily to them. In this manner, the impact on QoL, from before to after the program, can be compared. Painful feet may limit functional ability and mobility among patients, and rehabilitation nurses need to be aware of these factors in order to develop rehabilitation programs. Soreness secondary to metatarsalgia may be reduced through debridement using a scalpel, which may additionally improve functional ability and should be considered to be a key factor in implementing a multidisciplinary approach for fall prevention.

Podiatrists, physical therapists and physicians, in collaboration with a multidisciplinary rehabilitative nursing program, may develop an environment in which knowledge about foot mechanics and footwear can be improved, so as to prevent improper conditions and improve patients' health-related QoL.

Regarding metatarsal pain management, physical rehabilitation may teach foot pain management skills and help patients to achieve better adherence to treatment and acquire more effective coping mechanisms. In this manner, the negative effects from foot pain can be minimized. Thus, nurses may have the responsibility to manage foot care and improve patients' QoL.

The impact of our results may be difficult to compare with that of other studies due to differences regarding criteria and methodological variations. To the authors' knowledge, there are no other reports in the literature regarding QoL and foot health among participants with different degrees of metatarsalgia. Nevertheless, there are various limitations to the present study that need to be acknowledged. First, a larger sample size and greater diversity of subjects from different countries would be beneficial for strengthening this study. In addition, this would help to identify differences relating to different cultures and the mechanisms involved. This highlights the need for additional studies in order to define rehabilitative nursing interventions that might improve patients' foot health-related QoL.

CONCLUSIONS

Among people suffering from metatarsalgia, their condition had a negative impact on foot health-related QoL. There were significant reductions in foot-specific and general health among patients with metatarsalgia, especially regarding secondary and iatrogenic metatarsalgia, in relation to matched healthy controls.

The findings presented here have important consequences for proper rehabilitative nursing care, control over foot conditions and prevention of the appearance or development of metatarsalgia, as key factors in the process of monitoring foot functionality.

REFERENCES

1. Bardelli M, Turelli L, Scoccianti G. Definition and classification of metatarsalgia. Foot and Ankle Surg. 2003;9(2):79-85. doi: 10.1016/S1268-7731(02)00002-4.
2. Vayas Díez R, Sánchez Hernández P, Ayala Rodrigo A, et al. Actualización en el Tratamiento de la Metatarsalgia según la medicina basada en la evidencia. Canarias Médica y Quirúrgica. 2011;8(24):21-3. Available from: http://hdl.handle.net/10553/5758. Accessed in 2018 (May 28).

3. Arie EK, Moreira NS, Freire GS, Dos Santos BS, Yi LC. Study of the metatarsal formula in patient with primary metatarsalgia. Rev Bras Ortop. 2015;50(4):438-44. PMID: 26401502; doi: 10.1016/j.rboe.2015.06.018.
4. Barouk P. Recurrent metatarsalgia. Foot Ankle Clin. 2014;19(3):407-24. PMID: 25129352; doi: 10.1007/s10354-016-0445-2.
5. Espinosa N, Brodsky JW, Maceira E. Metatarsalgia. J Am Acad Orthop Surg. 2010;18(8):474-85. PMID: 20675640.
6. Scranton PE Jr. Metatarsalgia: diagnosis and treatment. J Bone Joint Surg Am. 1980;62(5):723-32. PMID: 7391095.
7. Pardal-Fernández JML, Rodríguez-Vázquez M. Metatarsalgias y neuropatías del pie. Diagnóstico diferencial [Metatarsalgia and neuropathies of the foot. Differential diagnosis]. Rev Neurol. 2011;52(1):37-4. PMID: 21246492.
8. DuVries HL. Surgery of the foot. Academic Medicine. 1959;34(10):1055. Available from: https://journals.lww.com/academicmedicine/Citation/1959/10000/Surgery_of_the_Foot.38.aspx. Accessed in 2018 (May 28).
9. Dueñas L. Estudio del umbral de disconfort a la presión en el pie de las personas mayores [thesis]. España: Universidad de Valencia. Valencia; 2013. Available from: http://roderic.uv.es/handle/10550/32536. Accessed in 2018 (May 22).
10. Irwin TA. Management of Metatarsalgia and Lesser Toe Deformities. Foot Ankle Clin. 2018;23(1):xv-xvi. PMID: 29362038; doi: 10.1016/j.fcl.2017.10.003.
11. Haque S, Kakwani R, Chadwick C, Davies MB, Blundell CM. Outcome of Minimally Invasive Distal Metatarsal Metaphyseal Osteotomy (DMMO) for Lesser Toe Metatarsalgia. Foot Ankle Int. 2016;37(1):58-63. PMID: 26314303; doi: 10.1177/1071100715598601.
12. Dunn JE, Link CL, Felson DT, et al. Prevalence of foot and ankle conditions in a multiethnic community sample of older adults. Am J Epidemiol. 2004;159(5):491-8. PMID: 14977645.
13. Roddy E, Muller S, Thomas E. Onset and persistence of disabling foot pain in community-dwelling older adults over a 3-year period: a prospective cohort study. J Gerontol A Biol Sci Med Sci. 2011;66(4):474-80. PMID: 21106703; doi: 10.1093/gerona/glq203
14. Hermida GLF. Metatarsalgia propulsiva. Tratamiento con la osteotomía triple de Maceira. An Med (Mex) 2012; 57 (2): 118-122. Available from: http://www.medigraphic.com/pdfs/abc/bc-2012/bc122f.pdf. Accessed in 2018 (May 29).
15. Espinosa N, Maceira E, Myerson MS. Current concepts review: metatarsalgia. Foot Ankle Int. 2008;29(8):871-9. PMID: 18752791; doi: 10.3113/FAI.2008.0000.
16. Espinosa N, Brodsky JW, Maceira E. Metatarsalgia. J Am Acad Orthop Surg. 2010;18(8):474-85. PMID: 20675640.
17. Nery CAS. Metatarsalgias. In: Hebert S, Xavier R, Pardini Júnior AG, Barros Filho TEP. Ortopedia e traumatologia: princípios e prática. 4th ed. Artmed; Porto Alegre; 2009. ISBN-10: 8536317531; ISBN-13: 978-8536317533.
18. Mifsut Miedes D, Franco Peris E, Turowicz M, Subías López A, Cutillas Ybarra B. Osteotomía de Weil percutánea en el tratamiento de las metatarsalgias. Correlación clínico-radiológica. Revista Española de Cirugía Osteoarticular. 2009;44(237):30-5. Available from: http://roderic.uv.es/bitstream/handle/10550/40727/30-35.pdf?sequence=1&isAllowed=y. Accessed in 2018 (May 28).
19. Parada I, Santamaria A, Muriano J, et al. Complicaciones en el tratamiento quirúrgico del hallux rigidus. Rev Pie Tobillo. 2016;30(1):32-8. doi: 10.1016/j.rptob.2016.04.009.
20. Moreno Rodríguez J. Metatarsalgia. Semin Fund Esp Reumatol. 2012;13(4):130-3. doi.org/10.1016/j.semreu.2012.07.002.
21. Balanowski KR, Flynn LM. Effect of painful keratoses debridement on foot pain, balance and function in older adults. Gait Posture. 2005;22(4):302-7. PMID: 16274911; doi: 10.1016/j.gaitpost.2004.10.006.
22. Menz HB, Morris ME. Clinical determinants of plantar forces and pressures during walking in older people. Gait Posture. 2006;24(2):229-36. PMID: 16214340; doi: 10.1016/j.gaitpost.2005.09.002.
23. Ueshima K, Ishikawa-Takata K, Yorifuji T, et al. Physical activity and mortality risk in the Japanese elderly: a cohort study. Am J Prev Med. 2010;38(4):410-8. PMID: 20307810; doi: 10.1016/j.amepre.2009.12.033.
24. Landi F, Russo A, Cesari M, et al. Walking one hour or more per day prevented mortality among older persons: results from ilSIRENTE study. Prev Med. 2008;47(4):422-6. PMID: 18672001; doi: 10.1016/j.ypmed.2008.06.020.
25. Menz HB, Morris ME. Footwear characteristics and foot problems in older people. Gerontology. 2005;51(5):346-51. PMID: 16110238; doi: 10.1159/000086373.
26. Bus SA, Maas M, de Lange A, Michels RP, Levi M. Elevated plantar pressures in neuropathic diabetic patients with claw/hammer toe deformity. J Biomech. 2005;38(9):1918-25. PMID: 16023481; doi: 10.1016/j.jbiomech.2004.07.034.
27. Menz HB, Morris ME, Lord SR. Foot and ankle risk factors for falls in older people: a prospective study. J Gerontol A Biol Sci Med Sci. 2006;61(8):866-70. PMID: 16912106.
28. Mickle KJ, Munro BJ, Lord SR, Menz HB, Steele JR. ISB Clinical Biomechanics Award 2009: Toe weakness and deformity increase the risk of falls in older people. Clin Biomech. 2009;24(10):787-91. PMID: 19751956; doi: 10.1016/j.clinbiomech.2009.08.011.
29. Chang BC, Liu DH, Chang JL, Lee SH, Wang JY. Plantar pressure analysis of accommodative insole in older people with metatarsalgia. Gait Posture. 2014;39(1):449-54. PMID: 24119776; doi: 10.1016/j.gaitpost.2013.08.027.
30. Cuesta-Vargas A, Bennett P, Jimenez-Cebrian AM, Labajos-Manzanares MT. The psychometric properties of the Spanish version of the Foot Health Status Questionnaire. Qual Life Res. 2013;22(7):1739-3. PMID: 23065118; doi: 10.1007/s11136-012-0287-3.
31. Bennett PJ, Patterson C, Wearing S, Baglioni T. Development and validation of a questionnaire designed to measure foot-health status. J Am Podiatr Med Assoc. 1998;88(9):419-28. PMID: 9770933; doi: 10.7547/87507315-88-9-419.

32. Bennett PJ, Patterson C, Dunne MP. Health-related quality of life following podiatric surgery. J Am Podiatr Med Assoc. 2001;91(4):164-73. PMID: 11319246.
33. Landorf KB, Keenan AM. An evaluation of two foot-specific, health-related quality-of-life measuring instruments. Foot Ankle Int. 2002;23(6):538-46. PMID: 12095123; doi: 10.1177/107110070202300611.
34. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83. PMID: 1593914.
35. Irving DB, Cook JL, Young MA, Menz HB. Impact of chronic plantar heel pain on health-related quality of life. J Am Podiatr Med Assoc. 2008;98(4):283-9. PMID: 18685048.
36. Mitty E. Nursing care of the aging foot. Geriatr Nurs. 2009;30(5):350-4. PMID: 19818272; doi: 10.1016/j.gerinurse.2009.08.004.
37. Dawson J, Thorogood M, Marks SA, et al. The prevalence of foot problems in older women: a cause for concern. J Public Health Med. 2002;24(2):77-84. PMID: 12141589.
38. Hughes M. Fall prevention among older adults: is London ready for the NSF? Br J Community Nurs. 2002;7(7):352-8. PMID: 12131850; doi: 10.12968/bjcn.2002.7.7.10631.
39. Menz HB, Lord SR. Foot pain impairs balance and functional ability in community-dwelling older people. J Am Podiatr Med Assoc. 2001;91(5):222-9. PMID: 11359885.
40. Gines-Cespedosa A, Alentorn-Geli E, Sanchez JF, et al. Influence of common associated forefoot disorders on preoperative quality of life in patients with hallux valgus. Foot Ankle Int. 2013;34(12):1634-7. PMID: 23943654; doi: 10.1177/1071100713502321.
41. Morales-Muñoz P, De Los Santos Real R, Barrio Sanz P, et al. Gastrocnemius Proximal Release in the Treatment of Mechanical Metatarsalgia. Foot Ankle Int. 2016;37(7):782-9. PMID: 27036137; doi: 10.1177/1071100716640612.
42. Toepfer A, von Eisenhart-Rothe R, Harrasser N. Metatarsalgia: Differential diagnosis and therapy. Wien Med Wochenschr. 2017;167(11-12):285-92. doi: 10.1007/s10354-016-0445-2.

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What do Cochrane systematic reviews say about the use of cannabinoids in clinical practice?

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ABSTRACT

BACKGROUND: The therapeutic effects of cannabinoid compounds have been the center of many investigations. This study provides a synthesis on all Cochrane systematic reviews (SRs) that assessed the use of cannabinoids as a therapeutic approach.

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

METHODS: A broad search was conducted in the Cochrane Database of Systematic Reviews to retrieve any Cochrane SRs that assessed the efficacy and safety of cannabinoids as a therapeutic approach. The results and key characteristics of all reviews included were summarized and discussed.

RESULTS: Eight SRs were included. They assessed the use of cannabinoids for the following types of conditions: neurological (two SRs), psychiatric (two SRs), rheumatological (one SR), infectious (one SR) and oncological (two SRs). There was moderate-quality evidence showing that the use of cannabinoids reduced nausea and vomiting among adults, compared with placebo. Additionally, there was moderate-quality evidence showing that there was no difference between cannabinoids and prochlorperazine regarding the number of participants who reported vomiting, in this same population.

CONCLUSIONS: This review identified eight Cochrane systematic reviews that provided evidence of unknown to moderate quality regarding the use of cannabinoids as a therapeutic intervention. Further studies are still imperative for solid conclusions to be reached regarding practical recommendations.

INTRODUCTION

More than 500 natural compounds (including cannabinoids, terpenoids and alkaloids) have been identified in the cannabis plant. The recreational and therapeutic effects of cannabinoid compounds (there are nearly 100 of these compounds) have been the center of many investigations. The most common constituent of cannabis is delta-9 tetrahydrocannabinol (THC), the substance that is considered to be the primary psychoactive agent in cannabis.[1]

However, it has been hypothesized that not only THC but also a huge number of other cannabinoids (including synthetic analogues) such as cannabidiol, cannabinol, nabilone, dronabinol and levonantradol have therapeutic effects. The route of administration may play an important role in the effect that cannabis has, and this needs to be considered in designing health interventions. These possible routes involve smoking, vaporization, oral ingestion, passive exposure, intravenous injection and administration of rectal suppositories.[2]

In 2018, a committee designated by the National Academies of Sciences, Engineering and Medicine (NASEM) of the United States described the following as health-related endpoints from medical use of cannabis: therapeutic effects; mental health effects; cannabis abuse; problems relating to cannabis use; cardiometabolic risks; incidence of cancer; and death.[3]

A quick search for cannabis-related trials in the ClinicalTrials database (available at clinicaltrials.gov) in July 2018 showed that 432 studies are currently registered as trials in this database alone. Most of these are investigating the use of cannabis as an intervention for a variety of conditions, such as anxiety, pain, nausea and vomiting, depression and attention-deficit hyperactivity disorder.[4]

Despite the high amounts that have been invested in research on this topic, the relevance of cannabinoids as a therapeutic approach is still a matter of debate. Because these compounds may form a reasonable alternative for treating numerous conditions, it is imperative to assess the efficacy and safety of cannabinoids through well-designed and well-conducted randomized controlled trials.

OBJECTIVE

To present the evidence from Cochrane systematic reviews that assessed the therapeutic use of cannabinoids for any disease or condition.

METHODS

Design

This was a review of Cochrane systematic reviews.

Setting

This review was conducted within the Discipline of Evidence-Based Medicine of Escola Paulista de Medicina (EPM), Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP).

Criteria for including reviews

Types of studies

We included the latest version of full Cochrane systematic reviews (SR). We did not consider protocols or any SRs that had the status "withdrawn" in the Cochrane Database of Systematic Reviews (CDSR).

Types of participants

We considered participants with any clinical condition, regardless of age or sex.

Types of intervention

We considered any intervention derived from cannabis and its synthetic analogues. The cannabinoid compounds considered in these reviews included cannabidiol, cannabinol, nabilone, dronabinol, levonantradol and delta-9-tetrahydrocannabinol (THC), in any regimens or doses, when used for therapeutic purposes. We considered any pharmacological or non-pharmacological intervention as comparators.

Types of outcomes

We considered any clinical, social, laboratory or economic outcomes, as assessed and reported in the systematic reviews included.

Search for reviews

We conducted a broad systematic search in the Cochrane Database of Systematic Reviews (via Wiley) on July 10, 2018. The search strategy is shown in full in **Table 1**.

Selection of systematic reviews

Two researchers (RLP and COCL) independently read all the abstracts that were retrieved, to check their eligibility in relation to the inclusion criteria. Any disagreements during the selection phase were resolved by a third author (RR).

Presentation of the results

We produced a synthesis of the key results and characteristics of all the reviews included, using a narrative approach (qualitative synthesis).

For each SR included, we identified the respective population, intervention, comparator and outcomes (PICO); methods for searching for and selecting studies; methods for and results from critical assessment; methods for pooling results (meta-analytic approaches); quality of the body of evidence for each outcome; and applicability. In situations in which multiple interventions were addressed by a single SR, we considered only those that were relevant for the present study.

RESULTS

Search results

The initial search retrieved 139 systematic reviews (SRs). After the screening process, 8 SRs were included and brought together in the form of a synthesis of the data.[5-12]

Table 1. Search strategy in Cochrane Library

#1 MeSH descriptor: [Cannabinoids] explode all trees
#2 MeSH descriptor: [Cannabinol] explode all trees
#3 MeSH descriptor: [Cannabidiol] explode all trees
#4 MeSH descriptor: [Dronabinol] explode all trees
#5 MeSH descriptor: [Cannabis] explode all trees
#6 MeSH descriptor: [Cannabaceae] explode all trees
#7 Cannabinoids or Cannabinol or Cannabidiol or Dronabinol or "9-ene-Tetrahydrocannabinol" or "9 ene Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta(9)-Tetrahydrocannabinol" or "Tetrahydrocannabinol" or "Tetrahydrocannabinol, (6a-trans)-Isomer" or "Tetrahydrocannabinol, Trans-Isomer" or "Tetrahydrocannabinol, Trans Isomer" or "Tetrahydrocannabinol, (6aS-cis)-Isomer" or "Tetrahydrocannabinol, Trans-(+-)-Isomer" or "Tetrahydrocannabinol, (6aR-cis)-Isomer" or "THC" or (Cannabis) or Cannabis indica or Cannabis indicas or indicas, Cannabis or Cannabis sativa or Cannabis sativas or sativas, Cannabis or Medicinal Cannabis or Cannabis, Medicinal or Medical Cannabis or Cannabis, Medical or Cannabaceae
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
Filters: in Cochrane Reviews - Reviews

Results from systematic reviews

The SRs addressed the following types of conditions: neurological (n = 2),[6,7] psychiatric (n = 2),[5,9] rheumatological (n = 1),[12] infectious (n = 1)[8] and oncological (n = 2).[10,11] The main findings from the SRs included and the quality of the evidence (using the GRADE approach) are shown in **Table 2**. A brief summary of each SR is presented below.

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

Population/ clinical situation	Number of RCTs	Comparisons	Benefits and harm	Quality of evidence (GRADE approach)*
Dementia[7]	1		Study poorly reported – no conclusion could be drawn	NA
Epilepsy[6]	4	Cannabinoids plus antiepileptic drugs versus antiepileptic drugs alone.	Studies poorly reported – no conclusion could be drawn	NA
Fibromyalgia[12]	2	Dronabinol versus placebo Dronabinol versus amitriptyline.	Benefit of dronabinol • Pain reduction and better quality of life, compared with placebo • Better sleep pattern, compared with amitriptyline No difference in: • Pain, mood and quality of life, compared with amitriptyline • Fatigue and depression, compared with placebo Harm of dronabinol • Withdrawal due to adverse events • Adverse events	Very low Very low Very low Very low Very low Very low
HIV/AIDS patients[8]	7	Dronabinol versus placebo	No difference in: • Likelihood of gaining 2 kg of body weight or more	NA
Nausea and vomiting relating to chemotherapy among adults[11]	23	Cannabinoid versus placebo Cannabinoid versus prochlorperazine	Benefits of cannabinoid over placebo: • Complete absence of vomiting • Complete absence of nausea and vomiting • Withdrawal due to lack of efficacy Harm of cannabinoid • Withdrawal due to adverse event Benefit of cannabinoid over prochlorperazine: • Personal preference: people reported a preference for cannabinoids rather than prochlorperazine No difference between cannabinoid and prochlorperazine regarding: • Participants reporting no nausea • Participants reporting no vomiting • Complete absence of nausea and vomiting Harm of cannabinoid: • Withdrawal due to adverse event • Withdrawal due to lack of efficacy • Adverse events	Low Moderate Low Very low Low Low Moderate Low Low Very low NA
Nausea and vomiting relating to chemotherapy among children[10]	4	Tetrahydrocannabinol versus prochlorperazine/ metoclopramide Nabilone versus domperidone	Tetrahydrocannabinol versus prochlorperazine/metoclopramide for reducing nausea: conflicting results among studies included. Nabilone versus domperidone: benefit of cannabinoid for reducing nausea.	NA NA
Schizophrenia[9]	1	Cannabidiol versus amisulpride	No difference between interventions regarding: • Brief Psychiatric Rating Scale-E (BPRS) • Average overall score on Positive and Negative Syndrome Scale for Schizophrenia (PANSS) • Average negative symptom score on PANSS • Average positive symptom score on PANSS	NA NA NA NA
Tourette's syndrome[5]	2	delta-9-tetrahydrocannabinol (Δ9THC) versus placebo	A positive effect from Δ9THC was reported, but the improvements in tic frequency and severity were small and were only detected through some of the outcome measurements.	NA

RCT = randomized clinical trial; *GRADE (Grading of Recommendations Assessment, Development and Evaluation) aims to assess the quality of the body of evidence. Outcomes are assessed as presenting high quality of evidence (high confidence in results, i.e. the estimated effect is close to the true effect), moderate quality of evidence (it is very likely that the estimated effect is close to the real effect but there is possibility that it is not), low quality of evidence (confidence in the effect estimate is limited) or very low quality of evidence (the true effect is likely to be substantially different from the estimate effect).

Dementia

There is some evidence that the cannabinoid system may play a role during the regulation of neurodegenerative processes, including in relation to excessive glutamate production, oxidative stress and neuroinflammation. Neurodegeneration is a feature common to various types of dementia. These findings have led to interest in whether cannabinoids might be useful for treating dementia.

The objective of this review[7] was to assess the effects of cannabinoids for treating people with dementia. Only one randomized clinical trial (RCT) was included, and the results presented did not provide sufficient data to draw useful conclusions. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD007204.pub2/full.

Epilepsy

This review[6] aimed to assess the effects of cannabinoids as monotherapy or add-on treatment for epilepsy and included four RCTs, with 48 participants. Two RCTs were briefly reported as abstract or as letter to the editor. Anti-epileptic drugs were maintained in all studies. The four reports only assessed the secondary outcome of adverse effects. None of the patients in the treatment groups experienced any adverse effects.

Overall, the reports were very poor and precluded any conclusion relating to practice. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009270.pub3/full.

Fibromyalgia

Cannabis compounds have been used to reduce pain and other somatic and psychological symptoms.

This review[12] assessed the benefits and harm of cannabinoids for treating fibromyalgia symptoms in adults and included two RCTs (72 participants). Both of these studies used nabilone, a synthetic cannabinoid, at a bedtime dosage of 1 mg/day, in comparison with placebo or amitriptyline. Overall, the two studies presented moderate risk of bias. The evidence was derived from grouped mean data on completers (very low-quality evidence overall). The main findings were:

- Pain reduction: greater with nabilone than with placebo; no difference between nabilone and amitriptyline.
- Quality of life: better with nabilone than with placebo; no difference between nabilone and amitriptyline.
- Fatigue and depression: no difference between nabilone and placebo.
- Sleep pattern: greater improvement with nabilone than with amitriptyline.
- Mood: no difference between nabilone and amitriptyline.
- Withdrawal due to adverse events: higher in the nabilone groups (4/52 participants) than in the control groups (1/20 in placebo and 0/32 in amitriptyline group).
- Adverse events: the most frequent adverse events were dizziness, nausea, dry mouth and drowsiness (six participants in the nabilone groups). Neither study reported any serious adverse events.

It was concluded that there was no convincing unbiased high-quality evidence that might suggest that nabilone was useful for treating fibromyalgia. Moreover, its tolerability was low in this population. For further details, refer to the original abstract, available from: http://cochranelibrary- wiley.com/doi/10.1002/14651858.CD011694.pub2/full.

HIV/AIDS patients

There have been claims that cannabis improves the appetites of people with AIDS, results in weight gain and lifts mood, thus improving the quality of life.

This review[8] assessed the effects of cannabis (in its natural or artificially produced form), either smoked or ingested, on morbidity or mortality among HIV patients. Seven RCTs were included. The evidence that might suggest that cannabis use would have considerable effects regarding morbidity and mortality is currently limited. Data from a single RCT (n = 139, among which only 88 participants were evaluable) that had been conducted at a time before access to highly-active antiretroviral therapy (HAART) became available were assessed. It was found that dronabinol did not provide any benefit regarding the likelihood of gaining 2 kg in body weight or more (RR [risk ratio] 2.09; 95% CI [confidence interval] 0.72 to 6.06).

It was concluded that even though dronabinol has been registered by at least some medicine regulatory authorities for treatment of AIDS-associated anorexia, and even though some jurisdictions make allowances for "medical" use of marijuana by patients with HIV/AIDS, evidence to show that cannabis and cannabinoids would be effective and safe for this purpose is lacking. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD005175.pub3/full.

Nausea and vomiting relating to chemotherapy among adults

This review[11] assessed the effects of cannabis-based medications for chemotherapy-induced nausea and vomiting among adults with cancer. In total, 23 RCTs, conducted between 1975 and 1991, were included. No trials involved comparison with newer antiemetic drugs such as ondansetron. The main results from comparisons are summarized below.

Cannabinoid versus placebo:

- Complete absence of vomiting: more frequent with cannabinoid (3 RCTs; 168 participants; RR 5.7; 95% CI 2.6 to 12.6; low-quality evidence);
- Complete absence of nausea and vomiting: more frequent with cannabinoid (3 RCTs; 288 participants; RR 2.9; 95% CI 1.8 to 4.7; moderate-quality evidence);
- Withdrawal due to adverse event: more frequent with cannabinoid (2 RCTs; 276 participants; RR 6.9; 95% CI 1.96 to 24; I^2 = 0%; very low-quality evidence);
- Withdrawal due to lack of efficacy: more frequent with placebo (1 RCT; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; low-quality evidence).

Cannabinoid versus prochlorperazine

- Participants reporting no nausea: no difference between groups (5 RCTs; 258 participants; RR 1.5; 95% CI 0.67 to 3.2; I^2 = 63%; low-quality evidence);
- Participants reporting no vomiting: no difference between groups (4 RCTs; 209 participants; RR 1.11; 95% CI 0.86 to 1.44; I^2 = 0%; moderate-quality evidence);
- Complete absence of nausea and vomiting: no difference between groups (4 RCTs; 414 participants; RR 2.0; 95% CI 0.74 to 5.4; I^2 = 60%; low-quality evidence);
- Withdrawal due to adverse event: more frequent with cannabinoid (5 RCTs; 664 participants; RR 3.9; 95% CI 1.3 to 12; I^2 = 17%; low-quality evidence);
- Withdrawal due to lack of efficacy: more frequent with cannabinoid (1 RCT; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; very low-quality evidence);
- Adverse events: dizziness (7 RCTs; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; I^2 = 12%), dysphoria (3 RCTs; 192 participants; RR 7.2; 95% CI 1.3 to 39; I^2 = 0%), euphoria (2 RCTs; 280 participants; RR 18; 95% CI 2.4 to 133; I^2 = 0%), "feeling high" (4 RCTs; 389 participants; RR 6.2; 95% CI 3.5 to 11; I^2 = 0%) and sedation (8 RCT; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; I^2 = 31%) were more frequent in the cannabinoid group;
- Personal preference: people reported a preference for cannabinoids rather than prochlorperazine (7 RCTs; 695 participants; RR 3.3; 95% CI 2.2 to 4.8; I^2 = 51%; low-quality evidence).

Comparisons with metoclopramide, domperidone and chlorpromazine showed weaker evidence, based on fewer trials and participants, for higher incidence of dizziness with cannabinoids. Two RCTs (141 participants) compared an antiemetic drug alone with cannabinoid added to the antiemetic drug and did not show any differences between the groups.

It was concluded that cannabis-based interventions might be useful for adults with refractory chemotherapy-induced nausea and vomiting. However, the methodological limitations of the RCTs reduced the confidence regarding these findings. Future research considering the current chemotherapy regimens and newer antiemetic drugs is likely to modify these conclusions. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009464.pub2/full.

Nausea and vomiting relating to chemotherapy among children

This review[10] assessed the effects of pharmacological interventions for controlling anticipatory, acute and delayed nausea and vomiting among children and young people (aged less than 18 years) who were about to receive or were receiving chemotherapy. In total, 34 RCTs were included, but only four were about cannabinoids. The main comparisons and findings are presented below.

- Tetrahydrocannabinol versus prochlorperazine/metoclopramide: two RCTs showed conflicting results and the heterogeneity of the studies included meant that no data could be pooled.
- Nabilone versus domperidone: cannabinoid showed benefit regarding reduction of nausea (nausea severity score 1.5 compared with 2.5; P = 0.0; scale from 0 [none] to 3 [worst]).

It was concluded that cannabinoids might be effective but that they produced frequent side effects. The current evidence relating to the use of cannabinoids for this purpose is too scarce for any sound conclusion to be reached regarding the implications for clinical practice. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD007786.pub3/full.

Schizophrenia

This review[9] assessed the effects of cannabinoids for symptom reduction in people with schizophrenia and included one RCT (39 participants) comparing cannabidiol with amisulpride. The main results are presented below.

- Brief Psychiatric Rating Scale-E (BPRS): no difference between the groups at 7 days (MD [mean difference] -1.50; 95% CI -6.54 to 3.54; 1 RCT; 39 participants), 14 days (MD 1.80; CI -4.61 to 8.21; 1 RCT; 39 participants), 21 days (MD 4.20; CI -4.24 to 12.64; 1 RCT; 34 participants) or 28 days (MD 1.10; CI -8.18 to 10.38; 1 RCT; 35 participants).
- Average overall score (Positive and Negative Syndrome Scale for Schizophrenia [PANSS], total endpoint; higher scores = poor): no difference between the groups at 14 days (MD 0.00; CI -10.10 to 10.10; 1 RCT; 39 participants) or 28 days (MD 0.40; CI -13.42 to 14.22; 1 RCT; 35 participants).
- Average negative symptom score (PANSS; higher scores = poor): no difference between the groups at 14 days (MD 1.20; CI -2.13 to 4.53; 1 RCT; 39 participants) or 28 days (MD 2.70; CI -0.92 to 6.32; 1 RCT; 35 participants).

- Average positive symptom score (PANSS; higher scores = poor): no difference between the groups at 14 days (MD 1.20; CI -1.85 to 4.25; 1 RCT; 39 participants) or 28 days (MD 0.60; CI -3.92 to 5.12; 1 RCT; 35 participants).
- Adverse events: poorly reported and no analyses were performed.

It was concluded that the evidence so far is insufficient to show that cannabidiol has any antipsychotic effect. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD004837.pub3/full.

Tourette's syndrome

Gilles de la Tourette syndrome is a developmental neuropsychiatric condition characterized by chronic motor and phonic tics. Currently, the drugs used for Tourette's syndrome either lack efficacy or are associated with intolerable adverse events.

This review[5] assessed the effects of cannabinoids for treating tics, premonitory urges and obsessive-compulsive symptoms (OCS), among patients with Tourette's syndrome. Two RCTs were included (28 participants), and these compared delta-9-tetrahydrocannabinol (Δ9THC), either as monotherapy or as adjuvant therapy, with placebo. One RCT was a double-blind, single-dose crossover trial and the other was a double-blind, parallel-group trial. Both RCTs reported that Δ9THC had a positive effect. The improvements in tic frequency and severity were small and were only detected through some of the outcome measurements.

It was concluded that so far there is not enough evidence to support the use of cannabinoids for treating tics and obsessive-compulsive behavior among people with Tourette's syndrome. For further details, refer to the original abstract, available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD006565.pub2/full.

DISCUSSION

This review included eight systematic reviews (SRs) that assessed the use of cannabinoids for neurological, psychiatric, rheumatological, infectious and oncological conditions. Only two of the SRs included assessed the overall quality of the evidence through using the GRADE approach. The only moderate-quality evidence found was related to the use of cannabinoids to treat chemotherapy-related nauseas and vomiting among adults, showing that the use of cannabidiol reduces nausea and vomiting among adults, in comparison with placebo. Additionally, there was moderate-quality evidence showing that there was no difference between cannabinoid and prochlorperazine regarding the number of participants who reported vomiting. All other evidence ranged in quality from low to very low. These findings were similar to those of a previous overview of SRs that addressed only the effects of cannabinoids for nausea and vomiting related to chemotherapy.[13]

The benefits and harm of any therapeutic intervention, including use of cannabinoids, need to be properly addressed through randomized controlled trials (RCTs). Thus, the scope of this review did not extend to presenting results from primary observational or animal experimentation studies. The results from such studies are more susceptible to bias and should always be taken to be exploratory. These studies may nevertheless be useful for guiding well-designed RCTs.

Regarding the implications for practice and research, the results presented in **Table 2** may provide guidance for therapeutic proposals. However, it is important to emphasize that, because of the low quality of the evidence, further well-conducted RCTs may change the conclusions regarding the effects of the interventions.

According to these Cochrane SRs, use of cannabinoids to treat medical conditions is not supported by high-quality evidence. The scarcity of data precludes any solid conclusions regarding the efficacy and, especially, the safety of cannabinoids as therapeutic interventions. Further updating of the presented Cochrane systematic reviews also needs to carefully assess the quality of evidence, in order to better support healthcare decisions.

CONCLUSION

This review identified eight Cochrane systematic reviews (SRs) that provided evidence of unknown to moderate quality regarding the use of cannabinoids as a therapeutic intervention. These SRs found moderate-quality evidence regarding (a) benefits provided by cannabinoids (compared with placebo) for reducing nausea and vomiting that related to chemotherapy among adults and (b) lack of difference between cannabinoids and prochlorperazine regarding the number of participants in this subgroup who reported vomiting.

REFERENCES

1. WHO. Cannabis plant and resin. Section 2: Pharmacology. WHO Expert Committee on Drug Dependence Pre-Review. 2018. Last accessed on July 10, 2018. Available from: http://www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/. Accessed in 2018 (Jul 31).
2. Van der Pol P, Liebregts N, Brunt T, et al. Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. Addiction. 2014;109(7):1101-9. PMID: 24628797; doi: 10.1111/add.12508.
3. Abrams DI. The therapeutic effects of cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report. Eur J Intern Med. 2018;49:7-11. PMID: 29325791; doi: 10.1016/j.ejim.2018.01.003.
4. Pertwee RG. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. Br J Pharmacol. 2009;156(3):397-411. PMID: 19226257; doi: 10.1111/j.1476-5381.2008.00048.x.

5. Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's Syndrome. Cochrane Database of Syst Rev. 2009;(4):CD006565. PMID: 19821373; doi: 10.1002/14651858.CD006565.pub2.
6. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database of Syst Rev. 2014;(3):CD009270. PMID: 24595491; doi: 10.1002/14651858.CD009270.pub3.
7. Krishnan S, Cairns R, Howard R. Cannabinoids for the treatment of dementia. Cochrane Database of Syst Rev. 2009;(2):CD007204. PMID: 19370677; doi: 10.1002/14651858.CD007204.pub2.
8. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev. 2013;(4):CD005175. doi: 10.1002/14651858.CD005175.pub3.
9. McLoughlin BC, Pushpa-Rajah JA, Gillies D, et al. Cannabis and schizophrenia. Cochrane Database of Syst Rev. 2014(10):CD004837. PMID: 25314586; doi: 10.1002/14651858.CD004837.pub3.
10. Phillips RS, Friend AJ, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database of Syst Rev. 2016;2:CD007786. PMID: 26836199; doi: 10.1002/14651858.CD007786.pub3.
11. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Syst Rev. 2015;(11):CD009464. PMID: 26561338; doi: 10.1002/14651858.CD009464.pub2.
12. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev. 2016;7:CD011694. PMID: 27428009; doi: 10.1002/14651858.CD011694.pub2.
13. Schussel V, Kenzo L, Santos A, et al. Cannabinoids for nausea and vomiting related to chemotherapy: Overview of systematic reviews. Phytother Res. 2018;32(4):567-76. doi: 10.1002/ptr.5975.

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A psychotic experience during adolescence: reasoning about differential diagnosis. Case report

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KEY WORDS:
Psychotic disorders.
Conversion disorder.
Schizophrenia.
Hallucination.
Child psychiatry.
Adolescent psychiatry.

ABSTRACT

CONTEXT: The aim of the present clinical review was to illustrate the diagnostic difficulty associated with psychotic experiences during adolescence, in the light of the multiplicity of circumstances interplaying during this period. It was also intended to illustrate the observation that not all hallucinations occur in the context of a declared psychotic disorder.

CASE REPORT: The patient was a 16-year-old adolescent girl who came to the Emergency Department of Coimbra Pediatric Hospital. On admission, she displayed mood and sensory perception disorders, with a bizarre gait abnormality. A diagnosis of conversion disorder was finally suggested, in accordance with the International Classification of Diseases, 10th edition.

CONCLUSIONS: Conversive hallucinations are rare in the psychiatric literature. This diagnostic hypothesis only gained consistency over a long period of follow-up within a child and adolescent psychiatry outpatient service, which was fundamental for appropriate diagnostic clarification. The authors discuss psychotic experiences that can arise from a neurotic setting and share the reasoning that was constructed in relation to the differential diagnosis. The psychogenesis and phenomenology of this young patient's conversive hallucinations and the therapeutic strategies adopted over the course of the follow-up are also discussed.

INTRODUCTION

Since there is no consensus regarding the definition of psychosis, one can try to define it, in general terms, as a disturbance of thought and sensory perception that negatively affects behavior and overall functioning.[1] Psychotic symptoms arise from different disorders and etiologies, as nonspecific phenomena.[2-4] The most pervasive of these are perhaps delusions, hallucinations, disorganization of thought, speech and behavior, and negative symptoms (blunted affect, alogia and avolition).[1-3] Minor psychotic symptoms are reported relatively often in the general population without, however, meeting the criteria for a clinical diagnosis of psychosis.[5] The most commonly described prodromal manifestations of a first psychotic episode are reduced attention and concentration, anergy, decreased will and motivation, depressed mood, sleep disturbances, anxiety, social withdrawal, distrust, irritability and deterioration of the ability to function.[6-8]

Studies conducted among adolescents have found that the prevalence of "psychotic experiences" in this age group is between 17 and 18%.[1] These are frequently associated with states of emotional disturbances (mood or anxiety disorders) and it has been stated that in 90% of these cases, no declared psychotic disorder is developed.[5,9] Psychotic experiences reported by young people are rarely interpreted as isolated and declared psychoses: in actual fact, they may throw light on the existence of neurotic psychopathology. Rigor in assessing the mental state and investment in a substantiated history obtained from different people and diverse sources of information, along with due respect for the potential of "adolescence" as a process of transition and maturation, appear to be of utmost importance.

Characteristically, adolescence is a period of profound change, and is thus a prime age for the onset of mental, emotional and relational disorders. During its development, the symptoms that occur leave room for doubt as to whether they refer to preclinical and prodromal signs of an existing psychotic illness or are simply physiological signs of puberty. Moments of discontinuity and rupture, emotional instability, identity crisis and intergenerational conflict are all part of normative adolescence.

In this developmental context, adolescents need to gradually acquire skills and abilities. Competence regarding self-regulation falls within this reasoning, and the relationship between the process of mood regulation and the development of psychosis appears to be of major relevance.

Success in mood regulation becomes easier within a context of adequate social development that is guided by proficiency in adaptive management of disruptive situations in everyday life.

Psychopathology results from difficulties in relation to adaptive mediation of stressor circumstances, thereby inhibiting or limiting the normative development process. Symptoms may be associated with psychological conflicts within development, that are normative and transient, and/or reactive to certain situations (separation from parents, change of school, birth of a sibling, response to aggression or other traumatic events, difficulties in academic activities, difficulties in interpersonal relationships, difficulties in dealing with frustrations or in regulating emotions, etc.), and which have a dynamic and interactive component that does not appear serious and is often observed during growth.

Along this line of reasoning, two major difficulties should arise immediately in the mind of a child psychiatrist: distinguishing what is pathological from what is normative; and establishing a diagnosis when justified.

The aim of the present clinical review was to illustrate the diagnostic difficulty associated with psychotic experiences during adolescence. It was also intended to illustrate the observation that not all hallucinations occur in the context of a declared psychotic disorder. The authors describe their thoughts on psychotic experiences that can arise from a neurotic setting, and share the reasoning that was constructed in relation to the differential diagnosis.

CASE REPORT

The patient was a 16-year-old adolescent girl in 10th grade when she presented to the Emergency Department of Coimbra Pediatric Hospital (in 2013), accompanied by her father. She did not have any relevant medical history, but the death of her mother in 2010 (as a victim of breast cancer) was cited as the greatest trauma of her childhood, a circumstance that she was having difficulties in coping with.

On admission, she displayed disturbances of mood and sensory perception, concurrently with a bizarre gait abnormality. She was assessed within the neurology and pediatrics sectors, and organic pathological conditions were ruled out through analytical evaluations, electroencephalogram (EEG) and computed tomography (CT) scans. Observation within the child and adolescent psychiatry sector was then requested.

From the first observation, high levels of vegetative anxiety stood out, along with depressive mood, high levels of expressed emotion, thoughts dominated by intrusive images from the day of her mother's funeral, changes in sensory perception (egosyntonic visual hallucinations) and behavior dominated by traits of perfectionism and obsessiveness. Her father mentioned that she was under a great deal of stress in the light of her upcoming school evaluations. No psychiatric family history was identified. A diagnosis of affective psychosis was considered, in accordance with the International Classification of Diseases, 10th edition[10] (ICD-10), and she was medicated with a low dose of an antipsychotic drug.

After about 15 asymptomatic days, the patient presented again to the Child Psychiatry Service with allopsychic disorientation, psychomotor agitation, disorganized speech broken by irrational laughter that was inconsistent with the mood, disorganized thinking, abnormalities of thought control and content, and bizarre egosyntonic visual hallucinations. A drug test on urine that was requested proved benign. After emergency administration of an antipsychotic drug, followed by short hospitalization for reassessment, a new evaluation of the patient's mental state was made. She was found to be cognizant, cooperative and focused. Contact was reserved and she showed hypomimia. Her emotions were consistent with mild depression and blunted affect. She did not continue to show abnormalities of thought and sensory perception. Her condition was relatively similar to her previous state and she had no memory of the episode. At this stage, a diagnosis of psychotic disorder with symptoms of schizophrenia was made, in accordance with ICD-10. It was concluded from the assessment that she should be monitored long-term. Her antipsychotic medication was then adjusted, accordingly.

The improvement seen in subsequent consultations was believed to be a response to medication. However, her father confided that the first day of medication coincided with attendance at a spiritual center. Her father was understandably wondering about what was having greater impact: the medication or the spiritual center. However, because they were committed to the therapeutic process, they suspended their visits to the spiritual center.

Over the course of the follow-up her father also confided having met a lady for whom he had nurtured special feelings, prior to the onset of the clinical picture. This matter was addressed in conversations with the patient, and she reported having distrusted and disliked this relationship, because she considered that it was disrespectful to her mother's memory.

During the treatment process, she was helped to diversify her range of strategies, and to identify and verbalize her concerns, through more adaptive management and regulation of her emotions. Structured cognitive-behavioral psychotherapy was used for an intervention regarding her traits of perfectionism and obsessiveness. Long-term observation (for about two years) of this adolescent showed favorable progression, with gradual reduction of antipsychotic medication. The antidepressant therapy was maintained, accompanied by individual and family psychotherapy. While reducing the antipsychotic medication, use of selective serotonin reuptake inhibitor (SSRI) antidepressants was gradually started and this was maintained for about a year.

Recent evaluation of her mental state revealed that the patient is now a self-aware adolescent (19-year-old) who is cooperative and focused, with very faint levels of vegetative anxiety. She was euthymic and had syntonic behavior. No abnormalities of thought

or sensory perception were identified. She displayed a more developed range of coping strategies, in particular regarding management of emotions relating to her mother. There remained traces of anxious, perfectionist and hypercritical behavior, but it had clearly improved. A diagnosis of conversion disorder was suggested, in accordance with ICD-10, which gained consistency over a long-term period of monitoring. The different mental state assessments conducted can be seen in **Table 1**.

DISCUSSION

In the present case, differential diagnoses were made between affective psychosis (F39; ICD-10), psychotic disorder with schizophrenic symptoms (F23.1; ICD-10) and conversion disorder (F44; ICD-10).

According to the ICD-10, the fundamental disturbance in affective disorders is a change in mood or behavior, usually towards depression (with or without associated anxiety) or towards elation. This change in mood is usually accompanied by a change in overall functioning and most of the accompanying symptoms are secondary or easily framed within the context of such changes. Affective psychosis falls within this context.

Around 15 days after the patient's initial presentation, a diagnosis of psychotic disorder with symptoms of schizophrenia was suggested. According to the ICD-10, this is an acute psychotic disorder in which hallucinations, delusions and disorders are obvious, but are markedly variable, changing from day to day or even from hour to hour. Emotional turmoil with intense transient feelings of joy and ecstasy, or anxiety and irritability, are often present. Despite psychotic and emotional symptoms, there are no criteria for manic, depressive or schizophrenic episodes. Long-term observation (more than one month) is decisive.

Dissociative disorders (conversion) all involve an apparent loss that is either complete or forms part of the normal integration between memories of the past, awareness of identity and immediate sensations and control of body movements. They are presumed to be psychogenic in origin and are temporally associated with traumatic, unresolved or intolerable events, or disturbed relationships. The term "conversion" implies that there is an unpleasant effect that is engendered by the problems and conflicts that the individual cannot solve and is somehow manifested with these symptoms. These tend to be limited in time, unless they result from unresolvable problems or severe interpersonal difficulties. With regard to pathophysiology, conversion symptoms are due to unconscious repression of emotional conflicts, but there is a danger of misdiagnosis without a thorough medical workup.[11]

On admission, our patient displayed disturbance of mood and sensory perception, concurrently with a bizarre gait abnormality. She was assessed within the neurology and pediatrics sectors, and organic pathological conditions were ruled out. In the literature, conversion disorder is considered to be a relatively rare cause of walking disability. Thus, a few cases presenting alteration of gait in the context of conversion have been described.[12-15] Conversion disorder has been found to be the third largest underlying psychological cause of psychogenic motor disorder after depression and anxiety. However, detailed descriptions of hallucinations as a conversion symptom are even rarer in the psychiatric literature. We found only a few case reports in the literature, mostly from the middle to final decades of the twentieth century.[16-24] In 1982, Rack cited a case of hysterical hallucination and commented that among Asian women, especially teenagers, the commonest cause of hallucinations is hysteria and not schizophrenia.[25] These cases shared the circumstance of involving female patients, either adolescents or young adults.

In our case, different situations of conflict were identified and managed. Therapeutic interventions were successful and the patient has recovered. Long-term observation revealed an improved state with better emotional management and a broader range of coping strategies. Remission was achieved through behavioral and psychotherapy, while antipsychotics were gradually suspended.

Table 1. Mental state assessments

Assessments	Signs and symptoms	Diagnostic hypothesis
First assessment (first consultation)	Cognizant, cooperative and oriented (time and space) High levels of vegetative anxiety Depressive mood High levels of expressed emotion Anguish – "Did my mother suffer...?" (*sic*) Recurrent dreams and intrusive images from the day of the funeral Bizarre egosyntonic visual hallucinations Traits of perfectionism and obsessiveness	Affective psychosis (F39 – ICD-10)
Second assessment (second consultation, after 15 asymptomatic days)	Allopsychic disorientation Psychomotor disinhibition Disorganized speech Infantilized, hyperthymic Mood incongruent laughter Disorganized thinking, derealization Changes to thought control and content Bizarre egosyntonic visual hallucinations Not self-aware	
Third assessment (third consultation, after antipsychotic administration)	Cognizant, cooperative and focused Reserved contact Facial hypomimia Expressed emotions congruent with sub-depressive mood Blunted affect No changes in thought or sensory perception Self-aware, no recall for the episode	

The patient's condition was not considered to be part of an organically-based psychotic process. She will probably require long-term psychotherapy focusing on helping her to gain insight regarding her problems and hopefully making permanent changes for the better in both her symptoms and her personality structure.

We reviewed the literature in MEDLINE, Embase and LILACS using the English keywords "conversion disorder", "psychotic disorder", "schizophrenia", "hallucinations", "adolescent psychiatry" and "child psychiatry", and the Portuguese keywords "transtorno conversivo", "transtorno psicótico", "esquizofrenia", "alucinações", "psiquiatria infantil" and "psiquiatria do adolescente". The results are presented in **Table 2**. We only found a few reports, mostly from the middle to final decades of the 20th century.

Table 2. Search of the literature in medical databases for case reports on conversion disorder with hallucinations. The search was conducted on October 10, 2016

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	conversion disorder AND psychotic disorder AND adolescent psychiatry AND "case reports" [Publication Type]	0	0
	conversion disorder AND psychotic disorder AND child psychiatry AND "case reports" [Publication Type]	0	0
	conversion disorder AND schizophrenia AND "case reports" [Publication Type]	1	2
	conversion disorder AND hallucinations AND "case reports" [Publication Type]	1	2
LILACS (via Bireme)	(transtorno conversivo [DeCs] OR conversion disorder [MeSH]) AND (transtorno psicótico [DeCs] OR psychotic disorder [MeSH]) AND (adolescência [DeCs] OR adolescence [MeSH]) AND "relato de caso"	0	0
	(transtorno conversivo [DeCs] OR conversion disorder [MeSH]) AND (esquizofrenia [DeCs] OR schizophrenia [MeSH]) AND (adolescência [DeCs] OR adolescence [MeSH]) AND "relato de caso"	0	0
	(transtorno conversivo [DeCs] OR conversion disorder [MeSH]) AND (alucinações [DeCs] OR hallucinations [MeSH]) AND "relato de caso"	2	2
Embase (via Elsevier)	conversion disorder AND psychotic disorder AND adolescent psychiatry AND "case reports" [Publication Type]	0	0
	conversion disorder AND psychotic disorder AND "case reports" [Publication Type]	0	0
	conversion disorder AND schizophrenia AND "case reports" [Publication Type]	1	1
	conversion disorder AND hallucination AND "case reports"	1	1

CONCLUSIONS

Conversion disorder is considered to be a relatively rare cause of walking disability, in the literature available. However, detailed descriptions of hallucinations as a conversion symptom are even rarer, with few case reports in the literature. Our diagnostic hypothesis only gained consistency over a long-term follow-up period within the context of our child and adolescent psychiatry outpatient service, which was fundamental for appropriate diagnostic clarification. It is also important to emphasize that there is a need for rigorous evaluation of the patient's mental state and investment in substantiated histories provided by different people and from various information sources.

REFERENCES

1. Monteiro P. Psicologia e psiquiatria da infância e da adolescência. Lisboa: Lidel; 2014.
2. Stevens JR, Prince JB, Prager LM, Stern TA. Psychotic disorders in children and adolescents: a primer on contemporary evaluation and management. Prim Care Companion CNS Disord. 2014;16(2).pii: PCC.13f01514.
3. Sidhu KAS, Dickey TO. Hallucinations in children: diagnostic and treatment strategies. Current Psychiatry. 2010;9(10):53-61. Available from: http://www.mdedge.com/currentpsychiatry/article/64056/schizophrenia-other-psychotic-disorders/hallucinations-children. Accessed in 2017 (May 10).
4. Joshi PT, Towbin KE. Psychosis in childhood ans its management. In: Davis KL, Charneu D, Coyle JT, Nemeroff C, editors. Neuropsychopharmacology – 5th generation of progress. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 613-24. [chapter 45]. Available from: https://www.acnp.org/asset.axd?id=e0a9ab37-d17d-4e40-bfa2-b776a214daae. Accessed in 2017 (May 10).
5. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med. 2009;39(2):179-95.
6. Klosterkötter J, Schultze-Lutter F, Ruhrmann S. Kraepelin and psychotic prodromal conditions. Eur Arch Psychiatry Clin Neurosci. 2008;258 Suppl 2:74-84.
7. Häfner H, an der Heiden W. The course of schizophrenia in the light of modern follow-up studies: the ABC and WHO studies. Eur Arch Psychiatry Clin Neurosci. 1999;249 Suppl 4:14-26.
8. International Early Psychosis Association Writing Group. International clinical practice guidelines for early psychosis. Br J Psychiatry Suppl. 2005;48:s120-4.
9. Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J. The incidence and outcome of subclinical psychotic experiences in the general population. Br J Clin Psychol. 2005;44(Pt 2):181-91.
10. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva: World Health Organization; 1993. Available from: http://www.who.int/classifications/icd/en/GRNBOOK.pdf. Accessed in 2017 (May 10).

11. Kozlowska K. The developmental origins of conversion disorders. Clin Child Psychol Psychiatry. 2007;12(4):487-510.
12. Fahn S, Williams DT. Psychogenic dystonia. Adv Neurol. 1988;50:431-55.
13. Grattan-Smith P, Fairley M, Procopis P. Clinical features of conversion disorder. Arch Dis Child. 1988;63(4):408-14.
14. Quane T, Chambers CV, Snyderman D. Conversion disorder presenting as gait disturbance in an adolescent. Arch Fam Med. 1995;4(9):805-7.
15. Balkuv E, Basaran R, Caliskan M. Gait disturbance as conversion reaction accompanying anorexia nervosa in a young adult: a case report and literature review. Journal of Scientific Research & Reports. 2014;3(4):583-91. Article no. JSRR.2014.005. Available from: http://www.journalrepository.org/media/journals/JSRR_22/2013/Dec/Balkuv342013JSRR6783_1.pdf. Accessed in 2017 (May 10).
16. Levinson H. Auditory hallucinations in a case of hysteria. Br J Psychiatry. 1966;112(482):19-26.
17. Farley J, Woodruff RA Jr, Guze SB. The prevalence of hysteria and conversion symptoms. Br J Psychiatry. 1968;114(514):1121-5.
18. Goodwin DW, Alderson P, Rosenthal R. Clinical significance of hallucinations in psychiatric disorders. A study of 116 hallucinatory patients. Arch Gen Psychiatry. 1971;24(1):76-80.
19. Modai I, Sirota P, Cygielman G, Wijsenbeek H. Conversive hallucinations. J Nerv Ment Dis. 1980;168(9):564-5.
20. Andrade C, Srinath S. True auditory hallucinations as a conversion symptom. Br J Psychiatry. 1986;148:100-2.
21. Sirota P, Spivac B, Meshulam B. Conversive hallucinations. Br J Psychiatry. 1987;151:844-6.
22. Kasckow J, Maltbie A. Conversion hallucinations in a patient with pseudohypoparathyroidism. Jefferson Journal of Psychiatry. 1989;7(2). Article 6. Available from: http://jdc.jefferson.edu/jeffjpsychiatry/vol7/iss2/6/. Accessed in 2017 (May 10).
23. Zain AM. True hallucination as conversion symptom--a case report. Med J Malaysia. 1990;45(l):74-7.
24. Spivak B, Livnat E, Weizman A, Rabinowitz S, Mark M. True conversive hallucinations. Psychopathology. 1991;24(1):19-24.
25. Rack P. Race, Culture and Mental Disorder. London and New York: Tavistock Publications; 1982.

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Inflammatory myofibroblastic tumor of the prostate after transurethral resection of the prostate with negative expression of anaplastic lymphoma kinase: a case report

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KEY WORDS:
Granuloma, plasma cell.
Inflammation.
Prostate.

ABSTRACT

CONTEXT: Inflammatory myofibroblastic tumors are a rare type of soft-tissue tumor. Inflammatory myofibroblastic tumors are characterized by rearrangements involving the anaplastic lymphoma kinase gene locus on 2p23.

CASE REPORT: We report the case of a 67-year-old Chinese male who presented with dysuria and fever. Magnetic resonance imaging showed an irregular prostatic mass with an isointense signal and obscure boundary. Histopathological evaluation showed that the mass consisted mainly of spindle-shaped cells. Immunohistochemical evaluation showed that the tumor cells were negative for anaplastic lymphoma kinase.

CONCLUSIONS: Inflammatory myofibroblastic prostate tumors are rare lesions with unclear etiology. The pathological diagnosis is very important.

INTRODUCTION

Inflammatory myofibroblastic tumors can be found in various parts of the body and are frequently identified in the lung or abdominal cavity of children and young adults. Inflammatory myofibroblastic tumors of the urinary tract present more often in kidneys. Prostatic inflammatory myofibroblastic tumors are extremely rare. Since the first case in 2012, only one further case of prostatic inflammatory myofibroblastic tumor has been reported in the literature.[1,2] The usual clinical presentation of inflammatory myofibroblastic prostate tumors consists of dysuria and acute urinary retention. Differentiation of inflammatory myofibroblastic prostate tumors from malignant prostate tumors through imaging and laboratory tests is difficult. A case of prostatic inflammatory myofibroblastic tumor observed after transurethral resection of the prostate to treat prostate hyperplasia in a 67-year-old man is presented in this report.

CASE REPORT

A 67-year-old Chinese male presented with dysuria and fever for a month. He had a history of transurethral resection of the prostate to treat prostate hyperplasia four years earlier. Laboratory tests such as blood count and urinalysis were within the normal range. His serum total prostate-specific antigen level was 8.49 ng/ml (normal reference range: 0.00-4.00 ng/ml) and his free prostate-specific antigen level was 1.42 ng/ml (normal reference range: 0.00-0.93 ng/ml).

Subsequently, multiple echoless masses and calcification were found using ultrasonography. Magnetic resonance imaging then demonstrated an irregular prostatic mass with an obscure boundary and isointense signal on T1 and T2-weighted images (**Figure 1A** and **Figure 1B**). The lesion showed obvious enhancement in the early phase, on a contrast-enhanced magnetic resonance imaging scan (**Figure 2**). Multiple enlarged lymph nodes were found in the right iliac vascular area and in the inguinal area bilaterally.

A transperineal biopsy of the prostate was performed on this lesion because the diagnosis was still unclear. Histopathological evaluation showed that the mass consisted mainly of spindle-shaped cells and a chronic inflammatory component consisting of plasma cells (**Figure 3A**). Immunohistochemical evaluation showed that the tumor cells were positive for myoepithelial markers, including desmin, calponin, vimentin, actin and smooth muscle actin (**Figure 3B-E**), but that they were negative for CD117, CD10, S100 and anaplastic lymphoma kinase (**Figure 3F**).

Based on the histological and immunohistochemical findings, a pathological diagnosis of inflammatory myofibroblastic tumor was made. No further specific treatment was provided. The patient was followed up for two years and no evidence of recurrence or metastasis was noted.

DISCUSSION

Inflammatory myofibroblastic tumors were once considered to be inflammatory pseudotumors, xanthogranulomas, plasma-cell granulomas or plasma-cell pseudotumors.[3] However, inflammatory myofibroblastic tumors and inflammatory pseudotumors are completely different pathological concepts with different pathological manifestations. Inflammatory pseudotumors are characterized by an inflammatory infiltrate consisting of lymphocytes,

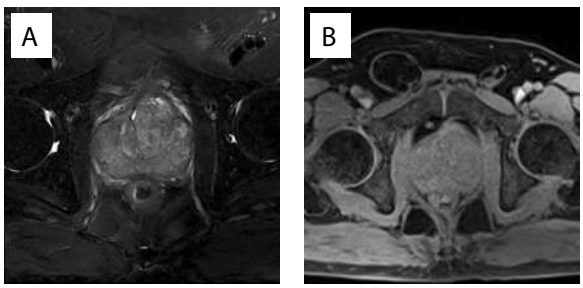

Figure 1. Irregular prostatic mass showing an isointense signal on T1-weighted images (A) and T2-weighted images (B), with an obscure boundary.

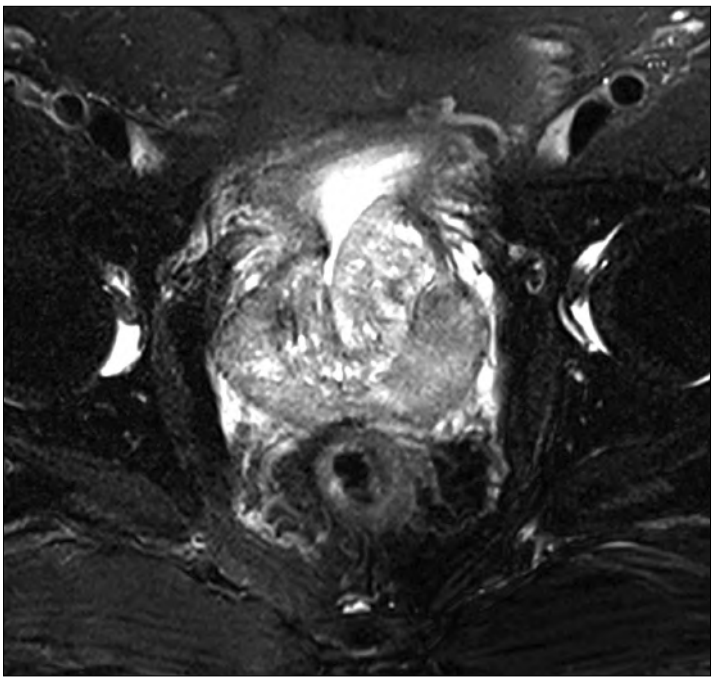

Figure 2. Contrast-enhanced magnetic resonance imaging showing clear enhancement in the early phase of the lesion.

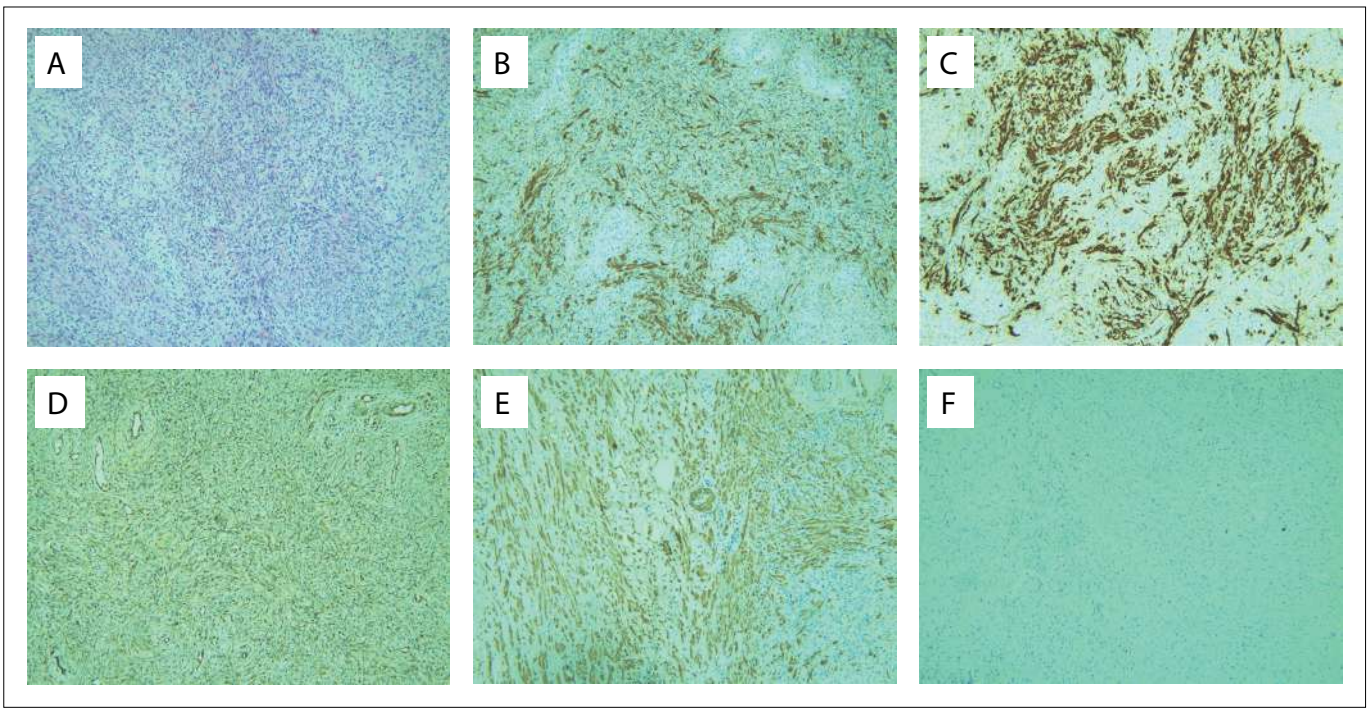

Figure 3. Histopathological and immunohistochemical sections through a prostatic inflammatory myofibroblastic tumor. The tumor consisted mainly of spindle-shaped cells and a chronic inflammatory component consisting of plasma cells (A); hematoxylin-eosin staining (× 100). Immunohistochemical sections showed that the tumor cells were positive for desmin (B), calponin (C), vimentin (D) and smooth muscle actin (SMA) (E), but were negative for anaplastic lymphoma kinase (ALK) (F).

plasma cells and histiocytes admixed with variable proportions of fibroblasts and myofibroblasts. On the other hand, inflammatory myofibroblastic tumors were classified as soft-tissue tumors by the World Health Organization in 2002, and consist mainly of differentiated myofibroblastic spindle cells, usually accompanied by numerous plasma cells, eosinophilic granulocytes and/or lymphocytes. Inflammatory myofibroblastic tumors are characterized by rearrangements involving the anaplastic lymphoma kinase gene locus on 2p23.[4]

The etiology of inflammatory myofibroblastic tumors remains unknown.[5] Inflammatory myofibroblastic tumors are frequently associated with inflammation, surgery and trauma. Therefore, inflammatory myofibroblastic tumors may be the body's response to injury caused by hyperplasia.

The neoplastic processes of inflammatory myofibroblastic tumors are characterized by gene rearrangement or fusion. Next-generation sequencing revealed that 85% of the cases evaluated harbored kinase fusions involving anaplastic lymphoma kinase, ROS1 or PDGFβ. The fusion partners identified thus far include the TPM3/4, CLTC and RANBP2 genes. A subset of anaplastic lymphoma kinase-negative inflammatory myofibroblastic tumors demonstrated ROS-1 gene fusions.[4,6]

Inflammatory myofibroblastic tumors can be found primarily in children and young adults, and they rarely occur in patients over 40 years old.[7] Although inflammatory myofibroblastic tumors are more commonly recognized in the lungs, they can also be observed in several other sites including the breasts, liver, spleen, thyroid, pancreas, urinary tract, peritoneum, retroperitoneum, lymph nodes, gastrointestinal tract and central nervous system.[8] Inflammatory myofibroblastic tumors of the urinary tract have been reported more often in the kidneys.

Prostatic inflammatory myofibroblastic tumors are extremely rare. Since the first case in 2012, only one further case of inflammatory myofibroblastic prostate tumor has been reported (**Table 1**).[1,2] In the present case, we reported that an inflammatory myofibroblastic tumor was found in an elderly man after transurethral resection of the prostate to treat prostate hyperplasia. This case was negative for anaplastic lymphoma kinase.

The final diagnosis of an inflammatory myofibroblastic tumor cannot be made from the features of the clinical manifestation, laboratory tests or radiological examination. The clinical manifestations of inflammatory myofibroblastic tumors are diverse in different sites. Urinary inflammatory myofibroblastic tumors present with obstructive symptoms such as dysuria, urinary frequency and urinary retention. Rectal examination may reveal a palpable mass. Inflammatory myofibroblastic tumors usually demonstrate low signal intensity on both T1 and T2-weighted images and show obvious enhancement on contrast-enhanced magnetic resonance imaging scans.[9]

However, these features are not distinctly different from those of prostate hyperplasia and prostate cancer. Therefore, the pathological diagnosis is especially important. These tumors are infiltrated by plasma cells, lymphocytic plasma cells, eosinophils and other inflammatory cells. Immunohistochemically, the spindle cells are positive for expression of muscle-derived proteins. Vimentin is often expressed diffusely, whereas smooth muscle actin and desmin are expressed focally or diffusely.[10]

This patient showed symptoms of dysuria, with abnormal prostate-specific antigen levels. A definite diagnosis cannot be made from symptoms, laboratory testing or imaging examinations. Ultimately, the diagnosis of an inflammatory myofibroblastic tumor was made using histological and immunohistochemical evaluations.

A variety of treatment methods for inflammatory myofibroblastic tumors have been reported, including chemotherapy, radiation therapy, non-steroidal anti-inflammatory drugs and glucocorticoid therapy. Additionally, there is no exact index to predict the risk of recurrence and metastasis.

Responses to the tyrosine kinase inhibitor crizotinib have been documented in patients with anaplastic lymphoma kinase-positive inflammatory myofibroblastic tumors. However, a new study by Lovly et al. found that this also had clear curative effects in patients with ROS1 fusion.[6] For extrapulmonary inflammatory myofibroblastic tumors, surgical excision is still preferred.[11,12] Coffin et al.

Table 1. Search of the literature in medical databases for inflammatory myofibroblastic tumor of the prostate. The literature search was conducted on July 28, 2017

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	#1 ("Granuloma, Plasma Cell"[Mesh]) #2 (Prostate"[Mesh]) #3 ("Transurethral Resection of Prostate"[Mesh]) #4 #2 OR #3 #5 #1 AND #4	3	2
Embase (via Elsevier)	#1(inflammatory myofibroblastic tumor) OR (inflammatory myofibroblastic tumour) OR (Granuloma Plasma Cell) #2 Prostate OR (Transurethral Resection of Prostate) #3 #1 AND #2	17	2
LILACS (via BVS)	#1 mh:(Granuloma, Plasma Cell) #2 mh:(Prostate) #3 mh:(Transurethral Resection of Prostate) #4 #2 OR #3 #5 #1 AND #4	2	1

BVS = Biblioteca Virtual em Saúde; LILACS = Literatura Latino Americana e do Caribe em Ciências da Saúde.

reported that negative expression of anaplastic lymphoma kinase correlated with a risk of recurrence and metastasis.[6,13,14] However, a review of extrapulmonary inflammatory myofibroblastic tumors documented a recurrence rate of 31% among anaplastic lymphoma kinase-negative tumors and 69% among anaplastic lymphoma kinase-positive tumors. Anaplastic lymphoma kinase gene rearrangements occurred in approximately 50-75% of cases of inflammatory myofibroblastic tumors.[7,15]

Neither of the previous reports of prostatic inflammatory myofibroblastic tumors measured anaplastic lymphoma kinase levels. One of these patients suffered from recurrence and distant metastasis and subsequently died.[1,2]

The patient of our report did not express anaplastic lymphoma kinase. No further specific treatment was provided. The patient was followed up for two years and no evidence of recurrence or metastasis was noted. This suggests that treatment approaches for inflammatory myofibroblastic tumor patients can vary and surgery may not be essential.

CONCLUSION

In conclusion, prostatic inflammatory myofibroblastic tumors are rare lesions with unclear etiology. A definitive diagnosis cannot be made from symptoms, laboratory testing and imaging studies. The pathological diagnosis is very important. Regarding treatment methods, although surgery is not essential for treating prostatic inflammatory myofibroblastic tumors that are negative for anaplastic lymphoma kinase expression, long-term follow-up is necessary.

REFERENCES

1. Zhang HH, Qi F, Zu XB, et al. Recurrence of inflammatory myofibroblastic tumor in bladder secondary to prostate treated with laparoscopic radical cystectomy. Med Sci Monit. 2012;18(8):CS63-66. PMID: 22847204.
2. Liu C, Zhao X, Zhao Z, et al. Malignant inflammatory myofibroblastic tumor of the prostate. J Clin Oncol. 2013;31(10):e144-7. PMID: 23401456.
3. Zhao HD, Wu T, Wang JQ, et al. Primary inflammatory myofibroblastic tumor of the breast with rapid recurrence and metastasis: A case report. Oncol Lett. 2013;5(1):97-100. PMID: 23255901.
4. Surabhi VR, Chua S, Patel RP, et al. Inflammatory Myofibroblastic Tumors: Current Update. Radiol Clin North Am. 2016;54(3):553-63. PMID: 27153788.
5. González MG, Vela D, Álvarez M, Caramés J. Inflammatory myofibroblastic duodenal tumor: A rare cause of massive intestinal bleeding. Cancer Biomark. 2016;16(4):555-7. PMID: 27002758.
6. Lovly CM, Gupta A, Lipson D, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. Cancer Discov. 2014;4(8):889-95. PMID: 24875859.
7. Zhou Y, Zhu J, Zhang Y, Jiang J, Jia M. An inflammatory myofibroblastic tumour of the breast with ALK overexpression. BMJ Case Rep. 2013. pii: bcr0720114474. PMID: 23386486.
8. Khanafshar E, Phillipson J, Schammel DP, et al. Inflammatory myofibroblastic tumor of the breast. Ann Diagn Pathol. 2005;9(3):123-9. PMID: 15944952.
9. Takayama Y, Yabuuchi H, Matsuo Y, et al. Computed tomographic and magnetic resonance features of inflammatory myofibroblastic tumor of the lung in children. Radiat Med. 2008;26(10):613-7. PMID: 19132493.
10. Gao F, Zhong R, Li GH, Zhang WD. Computed tomography and magnetic resonance imaging findings of inflammatory myofibroblastic tumors of the head and neck. Acta Radiol. 2014;55(4):434-40. PMID: 23966365.
11. Germanidis G, Xanthakis I, Tsitouridis I, et al. Regression of inflammatory myofibroblastic tumor of the gastrointestinal tract under infliximab treatment. Dig Dis Sci. 2005;5(2):262-5. PMID: 15745083.
12. Li HB, Xu YM, Yu JJ. Diagnostic puzzle of inflammatory pseudotumor of the urinary bladder: a case report with brief literature review. South Med J. 2010;103(6):563-6. PMID: 20710142.
13. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol. 2007;31(4):509-20. PMID: 17414097.
14. Teoh JY, Chan NH, Cheung HY, Hou SS, Ng CF. Inflammatory myofibroblastic tumors of the urinary bladder: a systematic review. Urology. 2014;84(3):503-8. PMID: 25168523.
15. Satomi T, Watanabe M, Matsubayashi J, Nagao T, Chiba H. A successfully treated inflammatory myofibroblastic tumor of the mandible with long-term follow-up and review of the literature. Med Mol Morphol. 2010;43(3):185-91. PMID: 20857269.

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Spontaneous rupture of right gastroepiploic artery aneurysm: a rare cause of hemorrhagic shock. Case report

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KEY WORDS:
Gastroepiploic artery.
Aortic rupture.
Shock, hemorrhagic.

ABSTRACT

CONTEXT: Aneurysms of the gastroepiploic arteries are seen only rarely. They are usually diagnosed during autopsy or laparotomy in patients with hemodynamic instability. Although the operation to treat this condition is relatively easy, delay in making the diagnosis affects the course of the disease.

CASE REPORT: A 57-year-old woman was admitted to the emergency department with abdominal pain and unconsciousness. A computed tomography scan showed extravasation of contrast agent at the head-corpus junction of the pancreas, and the patient underwent exploratory laparotomy under general anesthesia. During laparotomy, aneurysmatic rupture of the right gastroepiploic artery was detected. Control over bleeding was achieved by ligating the right gastroepiploic artery at its origin. The aneurysm was also resected and sent for pathological examination.

CONCLUSION: Especially in cases of unidentified shock, splanchnic artery aneurysms should be kept in mind. Moreover, in the light of the data in the literature, the possibility of death should be taken into account seriously and, if feasible, prophylactic aneurysmectomy should be performed.

INTRODUCTION

Aneurysms of the gastroepiploic arteries are seen only rarely.[1] They are usually diagnosed during autopsy or laparotomy in patients with hemodynamic instability.[2] Although the operation to treat this condition is relatively easy, delay in making the diagnosis affects the course of the disease.[3]

A 57-year-old woman was admitted to the emergency department with abdominal pain and unconsciousness. During laparotomy, aneurysmatic rupture of the right gastroepiploic artery was detected. In this study, the diagnosis and treatment of spontaneous right gastroepiploic artery rupture was discussed in the light of the literature (**Table 1**).

CASE REPORT

A 57-year-old female patient from whom written informed consent was obtained for publication of this manuscript was admitted to the emergency department with a history of abdominal pain of duration two days and slight confusion for the last six hours.

According to the patient's story, she had a history of atherosclerotic heart disease and hypertension. She was using angiotensin-converting enzyme (ACE) inhibitor, beta blocker and acetylsalicylic acid. She had a history of appendectomy, abdominal hysterectomy, laparoscopic cholecystectomy and incisional hernia operation.

On physical examination, the patient was confused but hemodynamically stable. On abdominal examination, there was diffuse tenderness and involuntary guarding. A rectal examination was unremarkable.

In the blood panel analysis, the white blood cell count was 20.6 x 10^3/µl, serum hemoglobin concentration 7.2 g/dl, platelet count 342 x 10^3/µl, hematocrit level 25.8%, creatinine level 4.2 mg/dl and blood urea nitrogen 50 mg/dl. Coagulation tests and other biochemical parameters were normal.

Following examination, resuscitation was started using crystalloid solutions and blood components, and abdominal ultrasound was performed. There was perihepatic, perisplenic and right paracolic free fluid. A computed tomography (CT) scan of the abdomen using intravenous contrast was then performed to search for possible sources of bleeding. In the CT scan,

extravasation of contrast agent at the head-corpus junction of the pancreas was observed.

The patient underwent exploratory laparotomy under general anesthesia (**Figures 1** and **2**). There was widespread hemoperitoneum and giant hematoma especially in the infrapyloric region. Approximately two liters of fresh blood and hematoma was evacuated from the peritoneal cavity.

The distal part of the stomach was transected using a linear stapler for better exposure. This revealed a ruptured right gastroepiploic artery aneurysm and retroperitoneal hematoma was also seen. Control of bleeding was achieved by ligating the right gastroepiploic artery at its origin. The aneurysm was also resected and sent for pathological examination. The operation was terminated after retrocolic gastrojejunostomy.

The CT scan was repeated to confirm that complete resection of the aneurysm and control of concurrent vascular anomalies had been achieved, before discharge (**Figure 3**). The patient was discharged on the sixth postoperative day without any complications.

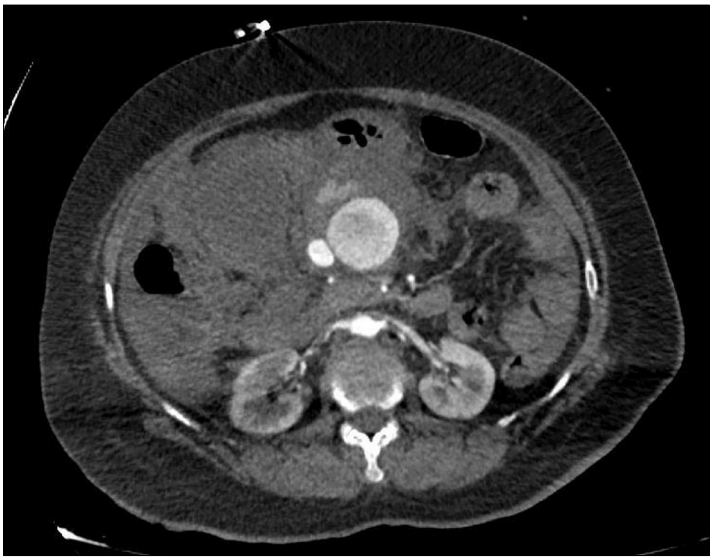

Figure 1. Preoperative late arterial phase computed tomography scan (axial) showing extravasation of intravenous contrast agent.

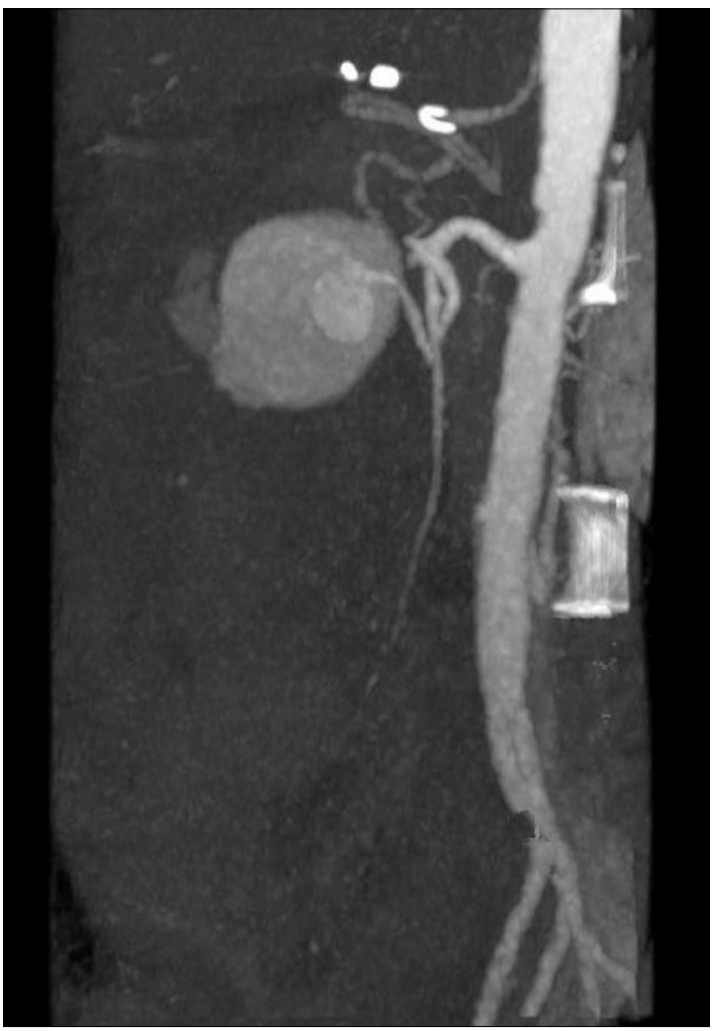

Figure 2. Preoperative computed tomography scan (three-dimensional) showing aneurysmatic rupture.

DISCUSSION

Idiopathic spontaneous intraperitoneal hemorrhage, which was first reported by Barber in 1909, was later referred to as abdominal apoplexy by Green and Powers.[4,5] It is a rare disease. In the study by Stanley and Zelenoch, 60% of the splanchnic artery aneurysms were reported to originate from the splenic artery, followed by 20% from the hepatic artery, 5.5% from the superior mesenteric artery, 4% from the celiac artery and 3% from the gastroepiploic artery.[6] In a study conducted by Pulli et al., only one out of 55 patients showed right gastroepiploic aneurysm, and this case was diagnosed incidentally during abdominal ultrasound.[7] As in the case presented here, right gastroepiploic artery aneurysm is among the rarest forms.

The precise mechanism is not fully known. However, weak tunica media and increased intravenous pressure are thought to be possible causes of rupture. Predisposing factors in the pathogenesis include arteriosclerosis, infection, medial necrosis, trauma, pregnancy and portal hypertension. To confirm the diagnosis,

Table 1. Results from search of the literature performed on April 4, 2017

Database	Search strategy	Results	
		Found	Related
MEDLINE (via PubMed)	right AND "gastroepiploic artery"[MeSH] OR "gastroepiploic" AND "artery" OR "gastroepiploic artery" AND "aneurysm"[MeSH] OR "aneurysm"	69	11
Scopus (via Elsevier)	right AND gastroepiploic AND artery AND rupture	44	11
LILACS (via Bireme)	(tw:(right gastroepiploic artery aneurysm))	0	-

pathological evaluation of the sacrificed specimen is required. In our patient, atherosclerosis was not seen but hypertension was present. Pathological examination of the lesion confirmed that it was a true aneurysm.

The symptoms of splanchnic aneurysm are usually nonspecific. There may be vague abdominal pain before the rupture. After the rupture, noticeable abdominal pain accompanied by hypotension is present. Shimada reported that the symptoms of ruptured and un-ruptured aneurysms differed.[8] In ruptured aneurysms, upper abdominal pain and hypovolemic shock were present, while in un-ruptured aneurysms, upper abdominal complaints were present. In our case, the patient's complaints were consistent with a ruptured aneurysm.

A ruptured aneurysm is usually diagnosed through laparotomy in a setting of hemodynamic instability. In less urgent cases, abdominal ultrasound examination, CT scans and angiography are helpful tools for making the correct diagnosis.

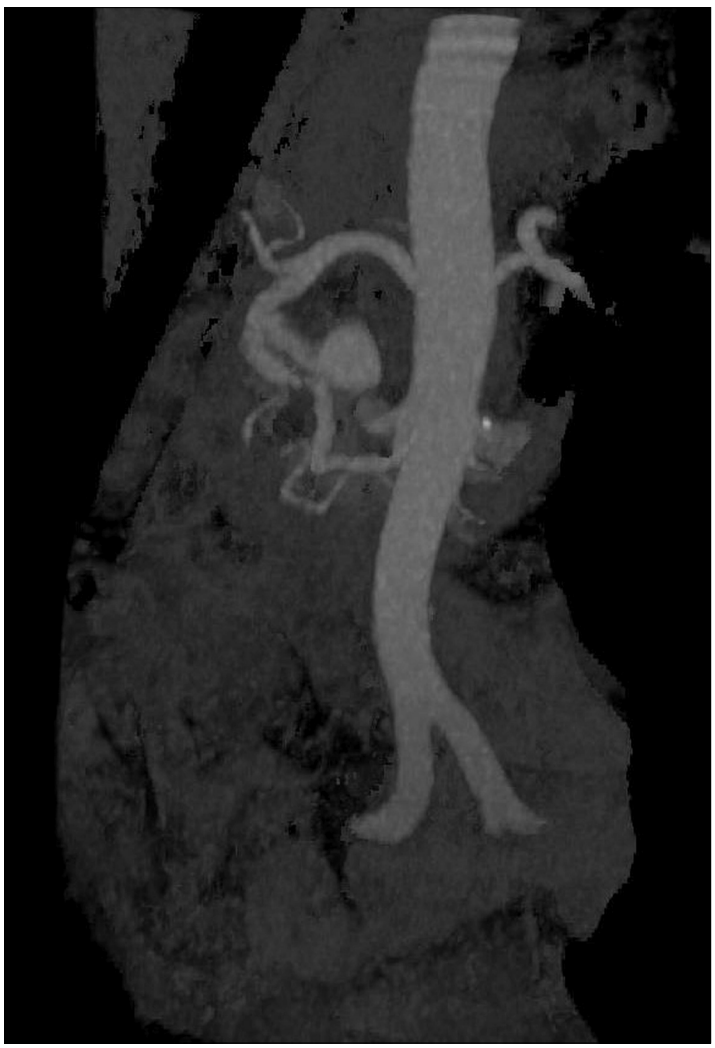

Figure 3. Postoperative computed tomography scan (three-dimensional) showing residual filling of the right gastroepiploic artery.

According to the literature, 81% of gastroepiploic artery aneurysms were diagnosed after rupture.[8] In Shimada's study, 44.4% of the patients were diagnosed by means of arteriography, while Morita et al. reported that angiography gave rise to a correct diagnosis rate of 64-76%.[9]

CT scans are the most important imaging test in the emergency setting. With CT scans, intravenous contrast is highly recommended and its effectiveness for locating active bleeding has been proven.[10] On the contrary, in our study, CT angiography scans did not show the location of the ruptured aneurysm precisely, but because of the extravasation, the patient underwent an operation.

In cases of hemorrhagic shock, the mainstays of treatment are volume resuscitation (either with fluid or with blood components) and control over life-threatening bleeding. In this context, for better exposure and rapid control of bleeding, the distal stomach was transected using a linear cutter stapler, at the expense of losing intactness of the upper gastrointestinal system. This made it easy to reach the pancreatic head and ligate the bleeding ruptured aneurysm. This procedure was undertaken despite lack of mention of this technique in the literature.

Surgical excision, which can be performed through conventional surgery or through laparoscopic surgery, provides complete disease control.[11] In emergency cases, operative mortality rates have been reported to be around 50-70%, while in elective cases this rate is 0-3%. If possible, the aneurysm should be ligated from the proximal side and the distal portion should be removed. According to the literature, this method is easy and carries low risk.[1] Transarterial catheter embolization is a non-surgical treatment method and can be performed promptly after angiography in patients with life-threatening hemorrhage. Hemostasis can be achieved easily through this. However, if the radiologist has no experience in this area and if technical difficulties occur, surgical treatment is usually required.

Regarding the follow-up of these patients, there is no consensus in the literature, given that most of the data are from case reports. A control radiological examination can be helpful after resection. If embolization is performed in elderly high-risk patients, observation is recommended.[1]

CONCLUSION

Especially in cases with unidentified shock, ruptures of splanchnic artery aneurysms should be kept in mind. Moreover, in the light of the data in the literature, the possibility of mortality should be taken into account seriously and, if feasible, prophylactic aneurysmectomy should be performed.

REFERENCES

1. Rohatgi A, Cherian T. Spontaneous rupture of a left gastroepiploic artery aneurysm. J Postgrad Med. 2002;48(4):288-9.

2. Kato R, Ishida H, Komatsuda T, Yagisawa H, Ishii T. Sonographic detection of an aneurysm of the gastroepiploic artery. J Clin Ultrasound. 2010;38(1):41-4.
3. Hassani KI, Bounekar A, Gruss JM. Spontaneous rupture of the right gastroepiploic artery: unusual cause of acute abdomen and shock. World J Emerg Surg. 2009;4:24.
4. Barber MC. Intra-abdominal haemorrhage associated with labor. Br Med J. 1909;2(2534):203-4.
5. Green WT, Powers JH. Intra-abdominal apoplexy. Ann Surg. 1931;93(5):1070-4.
6. Stanley JC, Zelenock GB. Splanchnic artery aneurysms. In: Rutherford RB, editor. 4th ed. Vascular surgery. Philadelphia: Saunders Company; 1995. p. 1124-39.
7. Pulli R, Dorigo W, Troisi N, et al. Surgical treatment of visceral artery aneurysms: A 25-year experience. J Vasc Surg. 2008;48(2):334-42.
8. Shimada H, Aoki A, Okazeri S, Kanai T, Ono T. A case of hemoperitoneum due to ruptured left gastroepiploic artery aneurysm. Japanese Practical Surgeon Society. 1993;54(12):3051-5. Available from: https://www.jstage.jst.go.jp/article/ringe1963/54/12/54_12_3051/_article. Accessed in 2017 (May 12).
9. Morita K, Ohmuma K, Urayama H, et al. Visceral artery aneurysm: report of eleven cases (in Japanese). Rinsho Geka (J Clin Surg) 1993;48:801-4.
10. Mortele KJ, Cantisani V, Brown DL, Ros PR. Spontaneous intraperitoneal hemorrhage: imaging features. Radiol Clin North Am. 2003;41(6):1183-201.
11. Uchikoshi F, Sakamoto T, Imabunn S, et al. Aneurysm of the right gastroepiploic artery: a case report of laparoscopic resection. Cardiovasc Surg. 1993;1(5):550-1.

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Cryptococcoma mimicking a brain tumor in an immunocompetent patient: case report of an extremely rare presentation

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KEY WORDS:
Cryptococcosis.
Brain neoplasms.
Meningitis, cryptococcal.
Immunocompetence.

ABSTRACT

CONTEXT: Central nervous system (CNS) infectious diseases have high prevalence in developing countries and their proper diagnosis and treatment are very important for public health planning. *Cryptococcus neoformans* is a fungus that may cause several CNS manifestations, especially in immunocompromised patients. Cryptococcal meningitis is the most common type of involvement. Mass-effect lesions are uncommon: they are described as cryptococcomas and their prevalence is even lower among immunocompetent patients. The aim here was to report an extremely rare case of cryptococcoma causing a mass effect and mimicking a brain tumor in an immunocompetent patient. The literature on CNS cryptococcal infections was reviewed with emphasis on cryptococcomas. Clinical, surgical and radiological data on a female patient with this rare presentation of cryptococcoma mimicking a brain tumor are described.

CASE REPORT: A 54-year-old female patient presented to the emergency department with a rapid-onset progressive history of confusion and completely dependency for basic activities. Neuroimaging showed a left occipital lesion and neurosurgical treatment was proposed. From histopathological evaluation, a diagnosis of cryptococcoma was established. She received clinical support with antifungals, but despite optimal clinical treatment, her condition evolved to death.

CONCLUSIONS: Cryptococcal infections have several forms of presentation and, in immunocompetent patients, their manifestation may be even more different. Cryptococcoma is an extremely rare presentation in which proper surgical and clinical treatment should be instituted as quickly as possible, but even so, there is a high mortality rate.

INTRODUCTION

Cryptococcosis is the most common fungal infection of the central nervous system (CNS) and it occurs mainly among immunocompromised patients.[1,2] Transmission occurs especially through inhalation of substances contained in the feces of pigeons and other birds.[1] It is usually considered to be a differential diagnosis among immunocompromised patients who present difficult-to-treat long-term meningitis.[1,3]

The lungs are the primary sites of infection. From there, *Cryptococcus* spreads through a hematogenous route and can affect many organs such as the liver and spleen. When this organism passes through the blood-brain barrier, it generally means that the host defenses are compromised. This may be due to human immunodeficiency virus (HIV) infection or to chronic conditions such as renal and vascular diseases.[1]

In rarer cases, *Cryptococcus neoformans* infection may be manifested as neurocryptococcoma, which is a granulomatous CNS lesion that may cause a mass effect.[3] Few cases have been reported and the differential diagnosis needs to include other neuroinfectious diseases and primary or metastatic tumors.[1,3] Dubey et al.[4] reported only three cases of neurocryptococcoma over a 23-year period, over which 40 granulomatous brain lesions were considered. The treatments included antifungal medications and, in many cases, surgical removal of the lesions.

Here, we describe a rare case of a female patient who did not have any condition that reduced her immunity. The only relevant occurrence in her medical history was the presence of controlled

arterial hypertension. She presented to the emergency department with a complaint of confusion that evolved very quickly to completely dependence for daily activities. Brain magnetic resonance imaging (MRI) showed mass-effect lesions in the left occipital lobe. She underwent neurosurgical intervention and meningitis treatment. Initially after surgery, she showed some neurological improvement. However, despite optimal treatment, her condition evolved to death.

CASE REPORT

A 54-year-old female patient presented to the neurosurgical emergency department, brought by her family, who described a history of rapid and progressive mental confusion (starting around two months earlier, with significant worsening over the last two weeks), leading to complete dependence for basic daily activities such as baths and eating. The only significant condition in her medical history was hypertension. One relevant social factor was that she had grown up on a farm and had had direct contact with several bird species including pigeons.

General and neurological physical examinations revealed that the patient was normotensive but in a poor general condition, was only able to obey simple orders, was restricted to bed (gait was not evaluated because the patient presented general weakness), seemed not to have any motor deficits and did not have any cranial nerves alterations or meningeal signs. It was difficult to perform a complete neurological examination because of her general condition. Based on her history and physical examination, she was categorized as having a score of 50 on the Karnofsky performance scale (KPS).

An MRI scan (**Figure 1**) performed on the patient a few days before this evaluation was brought with her and this showed two left occipital lesions surrounded by edema. She did not have any other systemic impairment. It was decided to perform surgery to resect these lesions, which had a macroscopic appearance of a solid component with more gelatinous pseudocyst areas inside. A quick check-up was performed, through laboratory tests, including a complete blood count before surgery, chest radiography and an electrocardiogram, and it did not show any abnormalities. Gross total removal was achieved and postoperative computed tomography (CT) scans were performed (**Figure 2**). In addition, samples from the lesion were sent for histopathological analysis (**Figure 3**). The result revealed that the lesion consisted of cryptococcoma. Because of this result, a more precise investigation was performed. The patient was found not to have either HIV or hepatitis (both tests were performed twice) or any other immunocompromised conditions. In addition, chest and abdominal CT scans were normal.

After the operation, the patient showed some neurological improvement and, after some days, a lumbar puncture was performed to evaluate the presence of meningitis. The presence of cerebrospinal fluid (CSF) infection was confirmed (large numbers of specimens of *Cryptococcus neoformans* were observed in the samples, along with increased protein levels). Before the puncture, a brain CT scan was performed to rule out any signs of intracranial hypertension or any alteration that might make it impossible to perform this procedure. All punctures revealed increased intracranial pressure (ICP) that progressively worsened (the highest value was 29 cmH_2O), but she did not present hydrocephalus.

Initially, ventriculoperitoneal shunt was not proposed, but when it was noticed that the ICP levels were progressively increasing and

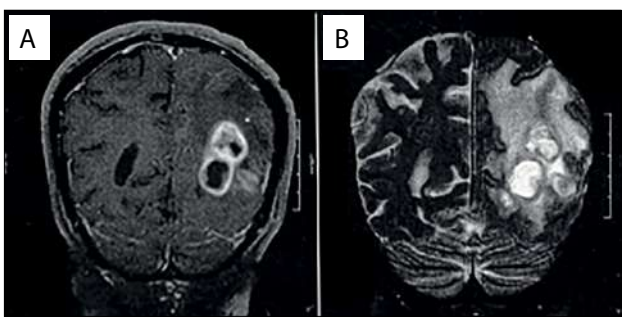

Figure 1. A) Coronal T1-weighted magnetic resonance imaging (MRI) showing enhanced left occipital lesions. B) Coronal T2 MRI showing extensive edema surrounding left occipital lesions.

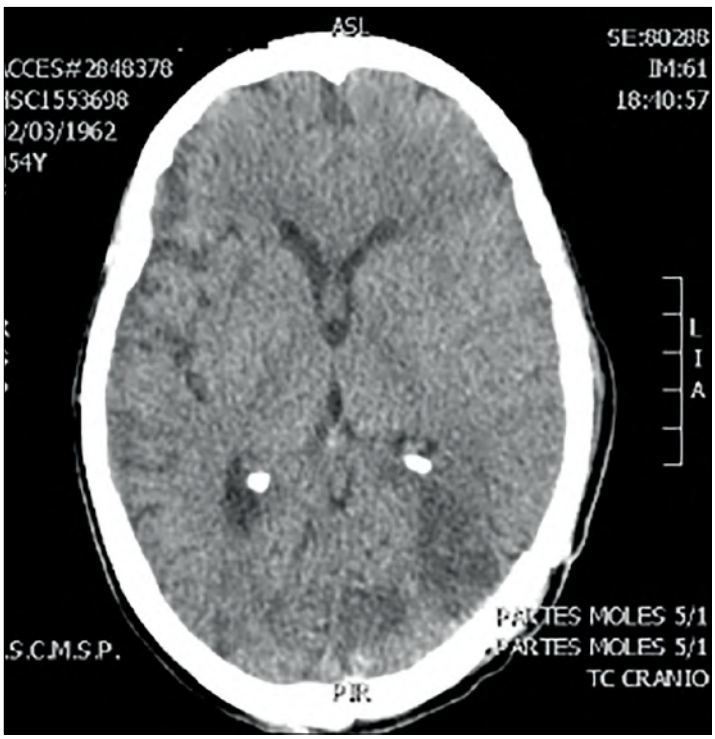

Figure 2. Axial computed tomography performed during the postoperative period showing gross total resection.

the procedure was indicated, she was seen to present a poor general condition with significant clinical impairment. Proper antifungal treatment consisting of amphotericin B (AmB) and fluconazole was administered, in association with clinical support, because she presented renal failure due to use of many drugs and required hemodialysis. However, despite optimal clinical treatment in the intensive care unit (ICU), comprising antifungal drugs, broad-spectrum antibiotics against pneumonia, electrolyte replacement, hemodialysis and respiratory physiotherapy, the patient's condition evolved to death due to various complications, including the initial disease, the toxicity of the various medications and bronchoaspiration leading to sepsis.

DISCUSSION

Cryptococcosis is the most common fungal disease of the central nervous system[1-4] and usually affects patients with a condition that reduces their immunological status. It therefore belongs to the group of opportunistic infections. It is most frequently associated with HIV infection[3] but patients with chronic renal disease, vascular conditions, hepatitis B or C, alcoholism, diabetes mellitus and oncological diseases are also typically more compromised than are immunocompetent patients, who rarely evolve with neurocryptococcosis.

Transmission occurs through inhalation of substances that are present in mammal and bird feces (pigeon feces have been described most frequently). Thus, the lungs constitute the entrance for the disease and pulmonary impairment is usually the first manifestation.[3] After the fungus enters the body, it can spread to several organs. The liver and spleen are generally affected[3] and, depending on immunological status, the infection can cross the blood-brain barrier through fungal neurotropism and cause neurological impairment.

Central nervous system cryptococcal infections usually manifest as meningitis, meningoencephalitis, encephalitis or ventriculitis.[5,6] These patients usually present with raised intracranial pressure and hydrocephalus, and require shunt procedures. Moreover, specific medications are required to institute the proper treatment. Amphotericin B is the first-line drug and flucytosine or fluconazole are secondary agents.[7] However, these drugs have severe side effects and, therefore, strict clinical follow-up is required. The main adverse effect is renal failure with electrolyte imbalance.

The World Health Organization (WHO) recommends two weeks of induction treatment with amphotericin B deoxycholate (AmBd) and flucytosine or fluconazole, followed by eight weeks of consolidation treatment with oral fluconazole.[8] Toxicity analyses on AmB administered at a dose within the currently recommended dose range of 0.7 to 1 mg/kg/day for treatment durations of 5 to 14 days, alone or combined with a second antifungal have been conducted.[7]

Nevertheless, in rare cases, this chronic granulomatous process can lead to formation of a mass (cryptococcoma) that has a tumoral appearance.[9] Metabolites released by *Cryptococcus* can inhibit the migration and function of leukocytes and promote survival and localized replication of the pathogen, thus facilitating chronic granulomatous inflammation and cryptococcoma formation.[6] There are a few reports of this condition, mainly in immuno-competent patients who usually did not develop this infection. A systematic review stored in the PubMed database was performed using the MESH terms cryptococcoma and neurocryptococcoma (**Table 1**). Twelve manuscripts described patients with cryptococcomas, but there were patients both with and without immunosuppressive conditions (**Table 2**).[4,9-19]

Surgical excision and debulking are indicated as adjunct therapies for lesions that are greater than or equal to 3 cm.[11,20] The type

Table 1. Search of the literature in medical databases for case reports on cryptococcomas. The search was conducted on May 5, 2017

Database	Search strategies	Papers found	Papers related
MEDLINE (Via PubMed)	"Brain Neoplasms"[Mesh] AND "Cryptococcosis"[Mesh] AND Case Reports[ptyp]	28	12

Table 2. PubMed-indexed papers in English reporting on cerebral cryptococcomas (MESH terms used: cryptococcoma; neurocryptococcoma)

Author and year	Number of patients	Immuno-suppression	Gender	Adulthood or childhood
Caldemeyer et al.,[12] 1996	1	No	Female	Child
Ho et al.,[11] 2005	1	No	Female	Adult
Kanaly et al.,[13] 2007	1	Yes	Male	Adult
Saigal et al.,[14] 2006	1	No	Male	Adult
Gologorsky et al.,[15] 2007	1	No	Male	Child
Sillero-Filho et al.,[9] 2009	1	Yes	Male	Adult
Patro et al.,[16] 2009	2	No	1 female and 1 male	Adult
Rai et al.,[18] 2012	1	Yes	Male	Adult
Jung et al.,[19] 2012	1	Yes	Male	Adult
Hagan et al.,[10] 2014	1	No	Female (puerperal)	Adult
Dubey et al.,[4] 2005	3	Yes	Male	Adult
Hiraga et al.,[17] 2015	1	No	Female	Adult

of neurological manifestation and the findings from neuroimaging depend on the patient's immunological status. Cryptococcomas are proportionally more likely to occur in immunocompetent patients than in immunosuppressed patients,[11,21] but in terms of absolute numbers, this is still an extremely rare condition that is initially difficult to diagnose.[21]

Intraparenchymal cryptococcomas usually present with low signal intensity on T1-weighted MRI and high intensity on T2-weighted images. Solitary cryptococcomas are very rare lesions.[22] However, despite these radiological hints, this is a very difficult diagnosis to make in non-immunocompromised patients without pulmonary impairment, before histopathological analysis has been conducted. At first, without any precisely known clinical history, these images give rise to other differential diagnoses, such as primary brain neoplasm (especially high-grade gliomas) and secondary lesions due to metastatic tumors. Other CNS infections such as tuberculosis are also diagnoses that need to be considered.

The patient of this paper was extensively investigated but did not have any immunosuppressive condition or pulmonary impairment. The only data that might have helped us to think of the diagnosis of cryptococcoma was the patient's previous contact with pigeons (which was not mentioned by the family until our team asked about this after the histopathological diagnosis had been established). Because the patient had a neurological dysfunction that developed quickly, which made us think initially that the cause was an aggressive brain tumor, it was decided to perform surgical removal. The histopathological analysis (**Figure 3**) confirmed all the typical alterations relating to cryptococcosis, and proper treatment was quickly instituted. However, this is a condition with elevated mortality, which also led to death in her case.

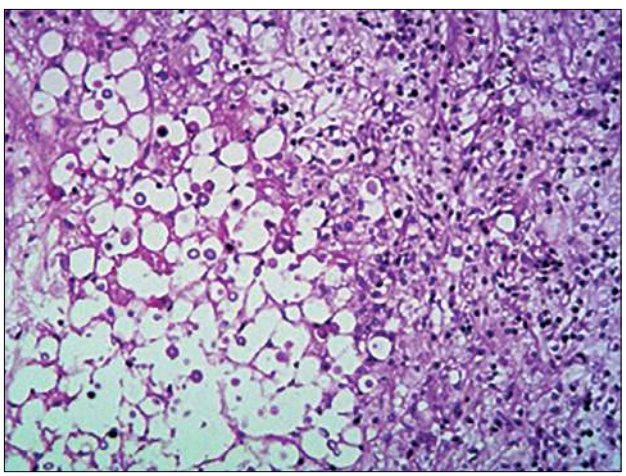

Figure 3. Histopathological analysis on the lesion. On the left side, the deeper part of the lesion shows multiple fungi. On the right side, there are multiple inflammatory cells. Hematoxylin-eosin staining; 40 x.

CONCLUSIONS

Diagnosing the tumoral form of cryptococcosis (cryptococcoma) in immunocompetent patients is a challenge even in endemic regions. Primary and secondary brain tumors are usually the first hypotheses in these cases. Proper investigation through anamnesis and imaging can lead to consideration of this diagnosis before the histopathological analysis has been conducted. A neurosurgical approach should be considered in cases of this type of mass lesion, to reduce the compressive factor and thus the intracranial pressure. Despite optimal treatment, this is a condition with high mortality.

REFERENCES

1. Awasthi M, Patankar T, Shah P, Castillo M. Cerebral cryptococcosis: atypical appearances on CT. Br J Radiol. 2001;74(877):83-5.
2. Berkfield J, Enzenberger W, Lanfermann H. Cryptococcus meningoencephalitis in AIDS: parenchymal and meningeal forms. Neuroradiology. 1999;41(2):129-33.
3. Klock C, Cerski M, Goldani LZ. Histopathological aspects of neurocryptococcosis in HIV-infected patients: autopsy report of 45 patients. Int J Surg Pathol. 2009;17(6):444-8.
4. Dubey A, Patwardhan RV, Sampth S, et al. Intracranial fungal granuloma: analysis of 40 patients and review of the literature. Surg Neurol. 2005;63(3):254-60; discussion 260.
5. Dubbioso R, Pappatà S, Quarantelli M, et al. Atypical clinical and radiological presentation of cryptococcal choroid plexitis in an immunocompetent woman. J Neurol Sci. 2013;334(1-2):180-2.
6. Gavito-Higuera J, Mullins CB, Ramos-Duran L, et al. Fungal Infections of the Central Nervous System: A Pictorial Review. J Clin Imaging Sci. 2016;6:24.
7. Bicanic T, Bottomley C, Loyse A, et al. Toxicity of Amphotericin B Deoxycholate-Based Induction Therapy in Patients with HIV-Associated Cryptococcal Meningitis. Antimicrob Agents Chemother. 2015;59(12):7224-31.
8. Alvarez-Uria G, Midde M, Pakam R, et al. Short-Course Induction Treatment with Intrathecal Amphotericin B Lipid Emulsion for HIV Infected Patients with Cryptococcal Meningitis. J Trop Med. 2015;2015:864271.
9. Sillero-Filho VJ, Souza ABM, Vaitsman RP, et al. Criptococoma cerebelar simulando neoplasia metastática [Cerebellar cryptococcoma simulating metastatic neoplasm]. Arq Neuropsiquiatr. 2009;67(2a):290-2.
10. Hagan JE, Ribeiro GS, Ko AI, et al. Puerperal brain cryptococcoma in an HIV-negative woman successfully treated with fluconazole: a case report. Rev Soc Bras Med Trop. 2014;47(2):254-6.
11. Ho TL, Lee HJ, Lee KW, Chen WL. Diffusion-weighted and conventional magnetic resonance imaging in cerebral cryptococcoma. Acta Radiol. 2005;46(4):411-4.
12. Caldemeyer KS, Mathews VP, Edwards-Brown MK, Smith RR. Central nervous system cryptococcosis: parenchymal calcification and large gelatinous pseudocysts. AJNR Am J Neuroradiol. 1996;18(1):107-9.

13. Kanaly CW, Selznick LA, Cummings TJ, Adamson DC. Cerebellar cryptococcoma in a patient with undiagnosed sarcoidosis: case report. Neurosurgery. 2007;60(3):E571; discussion E571.
14. Saigal G, Post MJ, Lolayekar S, Murtaza A. Unusual presentation of central nervous system cryptococcal infection in an immunocompetent patient. AJNR Am J Neuroradiol. 2005;26(10):2522-6.
15. Gologorsky Y, DeLaMora P, Souweidane MM, Greenfield JP. Cerebellar cryptococcoma in an immunocompetent child. Case report. J Neurosurg. 2007;107(4 Suppl):314-7.
16. Patro SN, Kesavadas C, Thomas B, Kapilamoorthy TR, Gupta AK. Uncommon presentation of intracranial cryptococcal infection mimicking tuberculous infection in two immunocompetent patients. Singapore Med J. 2009;50(4):e133-7.
17. Hiraga A, Yatomi M, Ozaki D, Kamitsukasa I, Kuwabara S. Cryptococcosis mimicking lung cancer with brain metastasis. Clin Neurol Neurosurg. 2015;135:93-5.
18. Rai S, Marak RS, Jain S, Dhole TN. Posterior fossa midline cryptococcoma in a patient with idiopathic CD4 lymphocytopenia. Indian J Med Microbiol. 2012; 30(3):367-70.
19. Jung A, Korsukewitz C, Kuhlmann T, et al. Intracerebral mass lesion diagnosed as cryptococcoma in a patient with sarcoidosis, a rare opportunistic manifestation induced by immunosuppression with corticosteroids. J Neurol. 2012;259(10):2147-50.
20. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50(3):291-322.
21. Vender JR, Miller DM, Roth T, Nair S, Reboli AC. Intraventricular cryptococcal cysts. AJNR Am J Neuroradiol. 1996;17(1):110-3.
22. Chen S, Chen X, Zhang Z, et al. MRI findings of cerebral cryptococcosis in immunocompetent patients. J Med Imaging Radiat Oncol. 2011;55(1):52-7.

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Fashion braces: an alarming trend

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Dear Editor,

Fixed orthodontic appliances, also known as braces, are apparatuses used for orthodontic treatment and are commonly used among teenagers. Certified orthodontists use braces to move unaligned teeth until they become well-arranged.

In Southeast Asian countries, the ratio of orthodontists to populace is much less than in many other countries; for instance, in Malaysia it is 1:220,000.[1] The limited number of specialists contributes towards inability to satisfy the demand. Thus, orthodontic treatment has become an expensive service in non-government clinics. Although the cost is less through government services, the waiting list is very long and most often only the patients with severe disorders will be selected. Hence, the high cost of treatments using braces confers luxury prestige to this apparatus. Moreover, use of braces is renowned for its connotation of spending power and therefore constitutes an alluring status symbol among teenagers across Southeast Asia.[2] This has resulted in a new trend for fashion braces, which are traded through the black market.

Fashion braces, also known as fake braces, look very comparable to real orthodontic braces but are not operative. They do not have any therapeutic purpose, but the black market for fashion braces targets teenagers who are seeking to attain the standard of luxury denoted by their use. Fashion braces can be supplied with a variety of ornamentation such as diamonds or cartoon characters attached to colorful orthodontic rubber bands.

Fashion braces are sold over the counter on the streets and online. Some websites and social-media platforms even provide do-it-yourself (DIY) videos. In some Southeast Asian countries, fake brace providers are mostly individuals who do not have orthodontic certification or qualification. They are not legally permitted to conduct dentistry practice and so they cannot register their offices. Without legal premises, they will usually arrange their customers' appointments in beauty salons[3] or at residential addresses.

These braces are affixed without proper clinical assessment and without any radiographic investigation prior to use. The availability of clinical apparatus and its hygiene status may be questionable especially in relation to DIY brace-fixing practices. Patients do not have any right to reclamation in the event of an injury, infection or any other issue during or after installation of the braces.

This substandard orthodontic practice can cause damage to patients' teeth, gums, lips and supporting bones. The authorities claim that these practices may also cause internal damage and cancer.[4] Moreover, there have been cases of teenagers who died after using fashion braces.[5] In the news this year (2018), some fashion braces have been found to present inferior material quality and have been laden with toxic heavy metals such as cadmium.[5]

The fashion-brace trend started in Southeast Asia and then expanded to the Far East. Recently, the trend reached the Middle East and it is still growing towards other parts of the world. Hence, it can be suggested that enforcement of laws and policies needs to be strengthened to monitor and prevent the use of fake braces. Higher authorities need to look at this issue seriously. Society needs to be made aware of the negative impact of fake braces, especially in relation to teenagers.

REFERENCES

1. Fong LF, Sivanandam H. Law allows dentists to carry out orthodontic treatment. The Star Online. 2016. Available from: https://www.thestar.com.my/news/nation/2016/09/12/law-allows-dentists-to-carry-out-orthodontic-treatment/#oWdjBtgeACIh0UeQ.99. Accessed in 2018 (Jul 23).
2. Rai AK. 'Zeena'- Practice or Malpractice? Primary Health Care. 2015;5:197. doi:10.4172/2167-1079.1000197.
3. Lacey MD. Brace yourself: Asian teenagers are wearing FAKE dental train tracks as a status symbol, but could they KILL their wearers? Mail online [Serial Online] 2013. Available from: http://www.dailymail.co.uk/femail/article-2256608/Fake-braces-trend-new-status-symbol-Asian-teenagers-KILL-wearers.html. Accessed in 2018 (Jul 23).
4. Kangwolkij P. Fad teeth braces banned. Bangkok Post [Serial Online] 2018. Available from: https://www.bangkokpost.com/news/general/1393506/fad-teeth-braces-banned. Accessed in 2018 (Jul 23).
5. Wipatayotin A. Doctors warn fashionable dental braces can kill. Bangkok Post [Serial Online] 2018. Available from: https://www.bangkokpost.com/news/general/1393582/doctors-warn-fashionable-dental-braces-can-kill. Accessed in 2018 (Jul 23).

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AIM AND EDITORIAL POLICY

Indexing and scope

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is now published bimonthly by the Associação Paulista de Medicina. It accepts articles in the fields of clinical health science (internal medicine, gynecology & obstetrics, mental health, surgery, pediatrics, epidemiology and public health). Articles will be accepted in the form of original articles, narrative reviews, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

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After receipt of the article through the electronic submission system, it will be read by the Editorial Team, who will check whether the text complies with the journal's Instructions for Authors. The Journal has adopted the CrossRef Similarity Check system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be rejected.

When the format of the manuscript is deemed acceptable, the Editorial Team will submit the article to the Editor-in-Chief who will assign at least two reviewers/referees with expertise in the theme, to assess it. The authors will then receive the reviewers' evaluation and will be required to provide all further information requested and the corrections that may be necessary. Changes to the text should be highlighted, accompanied by a letter answering the referees' comments, point by point.

Once the Editorial Team has received the revised manuscript, the text will be sent to the Editor-in-Chief for a decision. Manuscripts that are suitable for publication according to their scientific merit will be considered "accepted." However, all of them will subsequently be scrutinized to check for any problems regarding sentence construction, spelling, grammar, bibliographical references and other matters that may arise. The authors should contribute towards improving the manuscript by making it as readable as possible. Lastly, the Editorial Team will provide page proofs for the authors to approve. No article is published without this final procedure.

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3. a statement that implementation of the study was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles).
4. a brief description of contributorship.
5. a list of a minimum of five potential referees outside of the authors' institutions.

The Journal recommends that all articles submitted must comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (available at www.icmje.org).[1] This means that each type of study must be described in accordance with the specific quality guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9]

Abbreviations must not be used, even those in everyday use. Drugs or medications must be referred to using their generic names, avoiding casual mention of commercial or brand names. All drugs should be followed by the dosage and posology used. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses.

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The title page must contain:

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3. Full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full or omitted, without using abbreviations); his/her background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or undergraduate student); and his/her position currently held (for example, Master or Doctoral Student, Assistant Professor, Associate Professor or Professor, but not Head of Department, Dean, Provost or Rector), in the department and institution where he/she works, and the city and country (affiliations).
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The second page must include the title and a 250-word abstract in English (case reports with 100 words). Do not cite references in the abstract.

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1. Background: Describe the rationale for the study including the research question or the scientific hypothesis.
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Text

- Typical main headings include Introduction, Methods, Results, Discussion and Conclusion. The authors can use short subheadings too.
- Number the pages.
- Abbreviations must be avoided.
- A maximum of 3000 words in the main text, from the Introduction to the Conclusions; 1000 words for short communications.
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References

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

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Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent a resolution of 300 DPI and/or minimum size of 2500 pixels (width) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint or Microsoft Word documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Graphs prepared in Microsoft Excel (do not send them in image formats) spreadsheets must be accompanied by the tables of data from which they have been generated.

All the figures and tables should be cited in the text.

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded to indicate the magnification used. The staining agent should be specified in the figure legend.

Original articles

Clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis, are considered to be full-text original articles, with a maximum of 3000 words.

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles.

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion). The abstracts in short communications should not be structured and have a maximum of 100 words.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement[5,6]
2. Clinical trials: CONSORT Statement[2]
3. Accuracy studies on diagnostic tests: STARD Statement[8,9]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]
5. Case reports: CARE[7]

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials have only been accepted for publication if they have received an identification number from one of the clinical trial registers (the options are stated at http://www.icmje.org).

The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number in the PROSPERO database. Authors of randomized clinical trials and systematic reviews must thus register their studies before submitting them for publication in the São Paulo Medical Journal.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

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Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion), a maximum of five references and one figure or table. They should be structured in the same way as original articles. Individual case reports should contain the following sections: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

Both short communications and case reports must be submitted with abstracts and keywords. The abstracts in short communications should not be structured and have a maximum of 100 words.

The São Paulo Medical Journal is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[11] The search strategy for each database and the number of articles obtained from each database must be shown in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms are appropriate to be utilized for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT) the search dates should be indicated in the text or in the table.

Narrative reviews may be accepted by the São Paulo Medical Journal provided that a systematic search is made, and they should be structured as Original Articles. The search strategy and results should be presented as described above for case reports. By invitation from the Editor-in-Chief, narrative reviews addressing historical personal or collective experiences relating to clinical health sciences, epidemiology and public health may be accepted, but with no more than two authors.

Individual case reports should contain Introduction, Case Report, Discussion and Conclusion. Case reports should be structured in accordance with the norms of the CARE Statements.[7] Case reports published in São Paulo Medical Journal must be submitted with abstracts and keywords.

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Letters to the editor may address articles published in the São Paulo Medical Journal publication or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

DOCUMENTS CITED

1. Internal Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals, writing and editing for biomedical publications. Available from: http://www.icmje.org. Accessed in 2012 (Aug 6).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/consort-statement/. Accessed in 2012 (Aug 6).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet. 1999;354(9193):1896-900. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(99)04149-5/abstract. Accessed in 2012 (Aug 6).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: http://www.prisma-statement.org/index.htm. Accessed in 2012 (Aug 6).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2012 (Aug 6).
6. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: http://www.equator-network.org/reporting-guidelines/care/. Accessed in 2016 (Dec 20).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.stard-statement.org/. Accessed in 2012 (Aug 6).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90.
10. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contributors, Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed in 2012 (Dec 20).
11. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Available from: http://www.cebm.net/index.aspx?o=1047. Accessed in 2012 (Aug 6).

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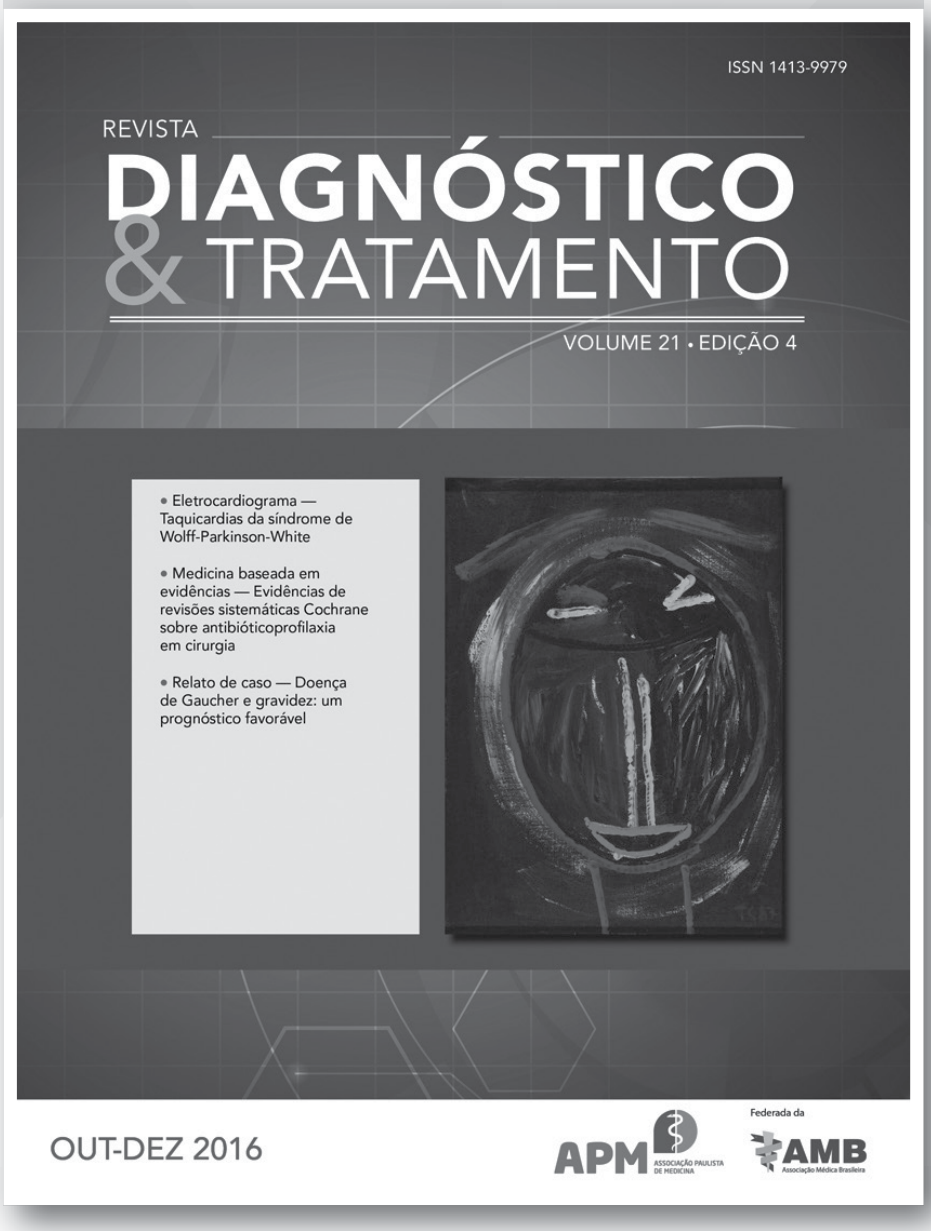

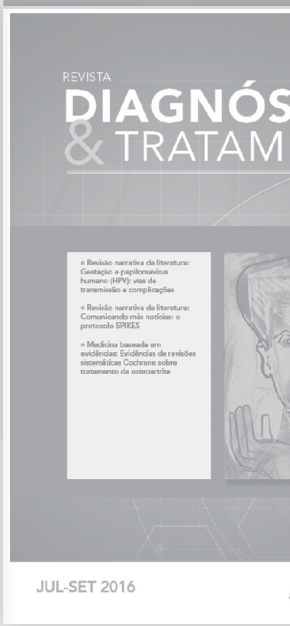

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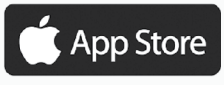

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