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Observational cross-sectional quantitative study:

- Breaking bad news: doctors' skills in communicating with patients

Cross-sectional study:

- Cognitive performance of premature infants: association between bronchopulmonary dysplasia and cognitive skills

Narrative review:

- Physical activity in Brazil: lessons from ELSA-Brasil

Cochrane highlight:

- What do Cochrane systematic reviews say about the clinical effectiveness of screening and diagnostic tests for cancer?

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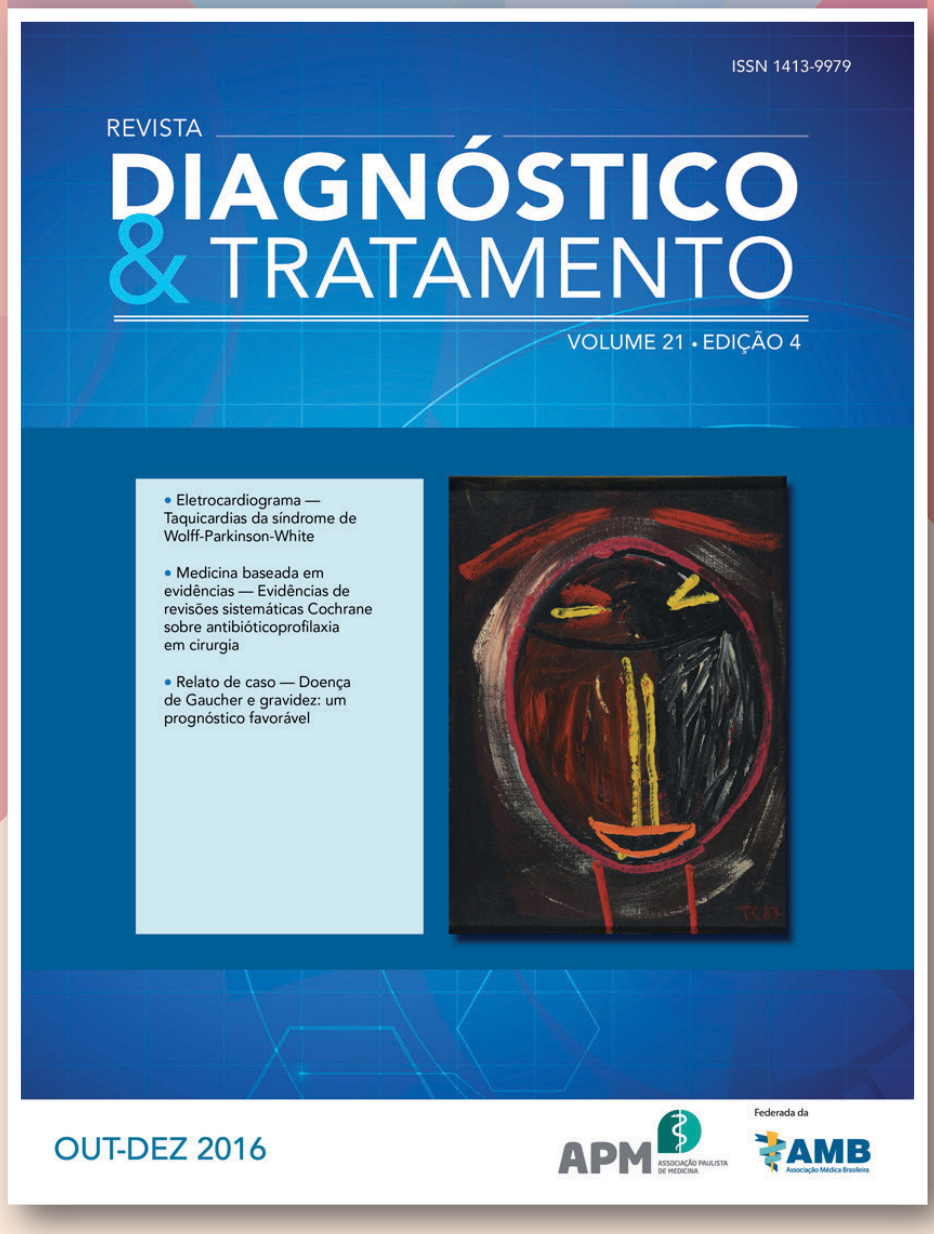

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Mental disorders and heart diseases: from William Harvey to today

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Coronary heart disease (CHD) is the leading cause of death worldwide.[1] Despite the decline in CHD mortality rates for all social strata in Brazil, the burden of disease remains higher among the poor than among the rich.[2] Nonetheless, since the 1950s, studies on cardiovascular epidemiology have successfully created a new agenda for this disease, which had until then been regarded as part of the fate of human existence or as an inescapable cause of death. In contrast to commonly held beliefs, these population-based studies showed that myocardial infarction and sudden cardiac death were the consequence of a myriad of identifiable causes.[3] Since then, new reasoning to explain disease frequencies that differ from those of communicable diseases (i.e. one disease linked to one pathogen) has emerged. This "myriad of causes" received the name "risk factors", which was the title of one of the first published papers communicating results from the Framingham Heart Study.[4]

The three major CHD risk factors of high cholesterol, hypertension and smoking habit have been well described since the 1960s.[5] However, it has taken decades to implement effective medical treatment for reduction of high cholesterol and hypertension on a wide scale, and it is still insufficient for less affluent people.[6] Despite warnings from the United States Surgeon General as early as 1963 and several actions coordinated by the World Health Organization, reduction of the smoking habit became a reality in the Western world only in the first decade of the 21st century. The reason for this was the strong resistance from the tobacco industry.[7]

One different approach towards explaining the rising incidence rates of CHD has come from an old idea linking the brain and the heart. When William Harvey described the circulatory system for the first time, during the 17th century, he warned that disorders of the brain or mental disturbances could impair the heart and the circulatory system.[8] Stress within individuals' daily lives has been correlated with heart diseases since the 1950s, but epidemiological tools to describe this are almost nonexistent.[9]

Two cardiologists in the United States launched the theory that one particular personality, the "type A behavioral pattern" was the cornerstone to understanding the CHD epidemic. Type A consisted of individuals who were highly competitive, ambitious, work-driven, time-conscious and aggressive. This theory was promptly accepted by the media after a famous book wrote by its proponents.[10] However, only two prospective studies corroborated this hypothesis; the results were negative in all other studies.[11]

The fall of the type A behavioral pattern theory was due not only to scientifically-based risk factors. The not-so-happy end of this hypothesis was the revelation of yet another instance of interference from the tobacco industry in academic fields. Since people with Type A were smokers more often than were other individuals, the Philip Morris company funded several types of research addressing the type A behavioral pattern. The aim was to show that the smoking habit was only an "intermediary factor", which was inserted in a pathway that had hypothetically begun with an unhealthy behavioral risk factor called type A and would end with myocardial infarction or sudden cardiac death.[12]

The type A behavioral pattern theory indeed helped the tobacco industry to avoid restrictions on cigarette advertising and sales. It also had a side effect: since this hypothesis linked CHD incidence to the behavior of rich white men, healthcare policy-makers worldwide did

not consider CHD to be a public health priority for a long time, because of the false inference that heart diseases are not frequent among less affluent people.

Researchers working on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) did not accept the type A behavioral pattern theory. Instead, they hypothesized that mental diseases are linked to heart disease, on the basis of several prospective studies addressing anxiety, depression and anger and their association with CHD.[13] The baseline evaluation of ELSA-Brasil revealed that anxiety was related to prevalent cardiovascular diseases,[14] to subclinical atherosclerosis (as measured from the intimal-media thickness of the common carotid artery)[15] and to coronary calcification.[16] Moreover, prescription of medicines for mental disorders was associated with low heart rate variability, which is a marker of adverse health outcomes.[17] The frequency of depression was correlated with presence of diabetes.[18]

In conclusion, mental health disorders should be a permanent variable to be added to all epidemiological studies addressing cardiovascular diseases.

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Breaking bad news: doctors' skills in communicating with patients

Dando más notícias: a habilidade dos médicos em se comunicar com os pacientes

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KEY WORDS:
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PALAVRAS-CHAVE:
Revelação da verdade.
Relações profissional-paciente.
Comunicação em saúde.
Comunicação para apreensão de informação.
Modelos educacionais.

ABSTRACT

CONTEXT AND OBJECTIVE: Breaking bad news is one of doctors' duties and it requires them to have some skills, given that this situation is difficult and distressful for patients and their families. Moreover, it is also an uncomfortable condition for doctors. The aim of this study was to evaluate doctors' capacity to break bad news, ascertain which specialties are best prepared for doing this and assess the importance of including this topic within undergraduate courses.

DESIGN AND SETTING: Observational cross-sectional quantitative study conducted at a university hospital in Belo Horizonte (MG), Brazil.

METHODS: This study used a questionnaire based on the SPIKES protocol, which was answered by 121 doctors at this university hospital. This questionnaire investigated their attitudes, posture, behavior and fears relating to breaking bad news.

RESULTS: The majority of the doctors did not have problems regarding the concept of bad news. Nevertheless, their abilities diverged depending on the stage of the protocol and on their specialty and length of time since graduation. Generally, doctors who had graduated more than ten years before this survey felt more comfortable and confident, and thus transmitted the bad news in a better conducted manner.

CONCLUSION: Much needs to be improved regarding this technique. Therefore, inclusion of this topic in undergraduate courses is necessary and proposals should be put forward and verified.

RESUMO

CONTEXTO E OBJETIVO: Dar más notícias, além de dever do médico, requer certas habilidades de sua parte, por se tratar de situação difícil e angustiante para o paciente e seus familiares, assim como desconfortável para os profissionais da saúde. O objetivo deste estudo é avaliar a capacidade dos médicos em dar más notícias, assim como as especialidades mais preparadas e a importância da inclusão do tema para a graduação.

TIPO DE ESTUDO E LOCAL: Estudo observacional, transversal, quantitativo, realizado em hospital universitário de Belo Horizonte, Minas Gerais, Brasil.

MÉTODOS: Este estudo utilizou de questionário baseado no protocolo SPIKES que foi respondido por 121 médicos deste hospital universitário. O questionário investigou suas atitudes, posturas, modos e medos em relação a dar más notícias.

RESULTADOS: A maioria dos médicos não teve problemas quanto ao conceito de más notícias, contudo, as habilidades divergiram dependendo da etapa do protocolo, assim como quanto a especialidade e tempo de formado. De modo geral, os médicos formados há mais de 10 anos se sentem mais confortáveis e confiantes, e transmitem tal informação de maneira mais bem conduzida.

CONCLUSÃO: Muito se tem a aprimorar em relação a essa técnica. Desse modo, a inclusão do tema durante a graduação é necessária e propostas devem ser sugeridas e averiguadas.

INTRODUCTION

The latest edition of the medical ethics code (2010: in chapter V, article 34) in Brazil states that doctors are forbidden from not telling the truth to patients about their diagnosis, prognosis, treatment risks and treatment goals. The only exception is information that could cause some damage to the patient, and in this case, the truth would have to be communicated through a legal representative. Thus, doctors have a legal duty to break bad news to patients and their families.[1]

The term "bad news" means any information that is given to patients and their families, which directly or indirectly reveals any negative or severe disorder that could change their future perspectives and vision of life.[2-6] Many difficulties that doctors have in breaking bad news can be explained by their fear of causing harm and suffering to their patients, and fear of being blamed for or having to deal with their patients' emotions. All of these emotions may be unpredictable and unexpected.[7] They may consist of denial, deep distress, blame or fear of emotions, diseases and death.[4,5] Although some studies have stated that patients want honesty, compassion, care and affectivity, and to have their doubts clarified by their doctors,[3] they also expect not only professionalism and competence in clinical skills, but also effectiveness of communication.[8] However, this should not be done in a cold or careless manner.[9] Thus, breaking bad news is difficult, unpleasant and uncomfortable. Nevertheless, it is truly necessary and requires skill on the part of healthcare professionals.[10]

To improve such skills, guidance on how to systematize breaking bad news and make it less traumatic has been provided.[2] One example of such techniques is the SPIKES protocol, which describes six steps of communication.[2,6,11] The first step "S", or setting up, refers to preparation of the medical environment. The place where such news is given should preferably be private, reserved and welcoming. This is the right moment to build a good doctor-patient relationship. The second step, "P", perception, is the opportunity to discover what the patient knows about his or her condition or disease, through open questions. The third step "I", invitation, is the moment to analyze how much the patient wants to know, and whether he or she has any doubts to be clarified. The fourth step "K", knowledge, is the time when everything about the diagnosis will be announced. At this moment, it is important to use simple words, without technical terms, in order to transmit the information. It is recommended that the matter should be introduced with some phrases that indicate that bad news will be transmitted. The fifth step "E", emotions, is the time to express empathy, identify the patients' emotions and give support. The last but not least important step "S", strategy and summary, is the time to suggest what the treatment should be, and what the prognosis is, and also to summarize everything that has been said, in order to check that patient has understood it.[2-6]

Studies have shown that doctors and healthcare professionals who take a training course on breaking bad news do not depend exclusively on their own experiences or observations, and they feel more comfortable and confident when communicating such information. Thus, holding workshops that teach techniques for breaking bad news will produce better prepared and more confident professionals.[9]

OBJECTIVE

To analyze doctors' skills and difficulties in breaking bad news, to ascertain which specialties are better prepared for this and to assess the importance of introducing this topic to undergraduate medical students.

METHODS

This was an observational and quantitative study conducted during 2015 and at the beginning of 2016, at a university hospital in Belo Horizonte, Minas Gerais, Brazil. The inclusion criterion for the subjects was that they should be doctors working in any sector of the university hospital. The following were excluded: doctors who did not have any contact with patients (radiologists, pathologists and laboratory workers), and those who did not sign the free and informed consent statement. The potential sample comprised the entire clinical staff of the hospital, including both residents and more senior doctors.

The research instrument used was a questionnaire structured into two parts (**Annex 1**). The first part consisted of five personal questions (the professional's full name, age, specialty, work sector and length of time since graduation). The second part consisted of 17 questions on bad news concepts, medical difficulties and emotions, the importance of including breaking bad news in undergraduate courses and how doctors should break bad news. Each question was based on the SPIKES protocol and on questionnaires in other studies that were based on the same protocol. This questionnaire has been internationally validated in Spanish, but Portuguese and English versions have been used in other studies.[8,11-13] All doctors answered the questionnaire and signed the consent statement within a 15-minute period at the hospital during their work time.

The hospital director signed a statement agreeing to the research. The data were gathered after the project had been approved by the research ethics committee at the School of Medical Sciences of Minas Gerais (Faculdade de Ciências Médicas de Minas Gerais, FCMMG).

The data were analyzed by means of the Epi-Info 7.1.2.0 software (2012) during October 2015 and February 2016, using frequencies, percentages and the chi-square test with significance of 0.05.

RESULTS

An up-to-date list provided by the university hospital showed that the clinical staff totaled 160 people, consisting of 42 residents

and 108 more senior doctors. Out of this total, 121 professionals provided responses for the survey (75% of the clinical staff). The remaining 25% did not participate for a variety of reasons: no direct contact with patients; unwillingness to participate; time mismatch between researcher and professional; vacation time for some professionals; or, in the view of some of the subjects, they were not responsible for delivering bad news. **Table 1** shows the distribution of the participating professionals according to their specialty.

Among the residents, the specialties that they belonged to were: internal medicine, surgery, anesthesiology and pediatrics. The sectors in which most of the professionals worked were surgical and intensive care units. The professionals interviewed were mostly aged 25 to 40 years (82%), with almost equal numbers of men and women.

In relation to the frequency with which these professionals gave bad news, the responses were uniform. Thus, most of them frequently (37.19%) or occasionally (28.10%) provided bad news. Moreover, most participants considered that their ability to communicate bad news was good or acceptable.

In the question on the concept of bad news, only one participant diverged from the opinion of the others. This individual believed that bad news was any information that caused physical harm to the patient. On the other hand, the response indicated by 99.17% of the participants was that bad news was any information that was transmitted with the implication of some serious negative change that could affect the individual's outlook on life or his/her prospects for the future.

Regarding questions relating to ideas proposed through the SPIKES protocol, we obtained the following patterns. Overall, 84.3% of the participants used both verbal and non-verbal language to deliver bad news. Among the participants who had graduated less than 10 years earlier, 75% used both types of language; among those who had graduated 11 to 20 years earlier, 78%; and among those who had graduated more than 20 years earlier, 100% (P = 0.64). Both types of language were used by only 64.71% of the surgeons, but by more than 77% of the other professionals. Comparing cardiology, nephrology and pediatrics (100%) and internal medicine (95.45%) with the other specialties, use of both types of language within these four specialties was much greater (P = 0.09).

Most of the professionals (about 78%) sought a cozy private place in which to provide the news. The medical specialties of those who looked for a private place to talk were distributed as shown in **Table 2**. Thus, nephrologists, surgeons and residents were better prepared regarding this topic than were professionals in other specialties (P = 0.0003).

Concerning length of time since graduation and the demand for privacy, most of the professionals with more than 20 years of experience sought a cozy private place (83.33%). On the other hand, those with less than 10 years of experience gave bad news to their patients more often in any available room (39.56%) than in a cozy private place (31.87%). This result was statistically significant (P = 0.02).

In relation to bedridden patients, 94.12% of the professionals provided bad news while standing next to the patient's bed. In relation to how professionals gave bad news, most of them spoke comprehensibly and clearly, while avoiding technical jargon, and they clarified doubts (**Table 3**).

93.39% of the participants provided information cautiously, according to the demands of the patients and/or their relatives, and they mostly (62.29%) told the truth first to the family and then to the patient. This was also seen with regard to the length

Table 1. Distribution of the medical professionals analyzed, according to their specialty

Specialty	Frequency	Percentage
Cardiology	7	5.79%
Surgery	17	14.05%
Internal medicine	22	18.18%
Intensive care	11	9.09%
Nephrology	7	5.79%
Orthopedics	15	12.40%
Pediatrics	4	3.31%
Medical residency	38	31.39%
Total	**121**	**100%**

Table 2. Relationship between specialty and the place where bad news is given

Specialty \ Place	Cozy private place	Using informal language in the hall/corridor or outside a room	In any available room	Total
Cardiology	0	4	3	**7**
Surgery	8	8	1	**17**
Internal medicine	6	10	6	**22**
Intensive care	5	4	2	**11**
Nephrology	3	1	3	**7**
Orthopedics	0	2	13	**15**
Pediatrics	2	0	2	**4**
Medical residents	22	2	14	**38**
Total	**46**	**31**	**44**	**121**

Table 3. How the professionals inform patients about bad news

Questions (Did the professional…)	Frequency	Percentage
Speak comprehensibly and clearly, while avoiding technical jargon?	104	85.95%
Offer details on the subject?	41	33.88%
Give hope to the patient even if there was none?	3	2.48%
Establish a trustworthy relationship?	39	32.23%
Offer technical details?	5	4.13%
Demonstrate empathy?	35	28.93%
Clarify doubts?	62	51.24%

of time since graduation: the majority also told the family first and then the patient.

Concerning the skills used when the professionals broke bad news, most of them always reserved a period for clarifying doubts (51.24%), and they listened carefully without interruptions (56.20%). Regarding the length of time since graduation, those who had graduated more than 20 years earlier were open to questions and to clarification of doubts in 83.33% of the cases, which was not seen among those who had graduated 11 to 20 years or 1 to 10 years earlier. Among the medical specialties, the ones in which significantly greater time was devoted to questions were cardiology and pediatrics (100% of the professionals) and surgery (88.24%).

Concerning exploration of what patients already knew about their condition, what they wanted to know and what their concerns were, more than 53% of the doctors took an approach of this nature among their patients.

Among the specialties, the professionals who most explored what patients already knew about their health condition were: surgeons (88.24%), general practitioners (77.27%), intensivists (100%) and pediatricians (75%). In relation to what patients wanted to know, 100% of cardiologists and 100% of pediatricians discussed this. Patients' concerns were explored by 72.73% of intensivists, 85.71% of nephrologists, 80% of orthopedists and 70.59% of first-year residents. With regard to the length of time since graduation, those with more than 10 years of experience explored these three areas most (**Table 4**).

Regarding the doctors' opinions about their fears and feelings, most of them felt sad (40.83%) when they had to break bad news. They were also afraid of being blamed (66.9%) and afraid of the patients' reactions (58.6%).

None of the participants was aware of any instrument or protocol that could help in addressing bad news and giving it to patients. Most of them had learned by watching other specialists (42.15%). The vast majority believed that adding the subject to undergraduate courses was important (45.45%) or very important (42.15%).

DISCUSSION

All patients, to a greater or lesser degree, are distressed when sick, because of the uncertainties about their real condition and prognosis. Therefore, doctors have a duty to contribute towards relieving this anguish and not to increase it through negative gestures or expressions (iatrogenesis). Consequently, doctors need to be prudent when communicating bad news, through using appropriate skills in order to avoid inappropriate non-verbal language.[13] In the context of non-verbal reactions, doctors' physical appearance, use of white clothes or a white coat and attentiveness to behavioral attitude positively influence the degree of confidence that patients have in their doctor.[14] Attitudes like making eye contact, touching hands or smiling, and expressing an empathic silence assure patients that they can count on the doctor during their period of distress. On the other hand, doctors should be prepared through adequate training and choosing apt skills, to be able to break bad news appropriately.[15]

Most of the professionals surveyed in the present study had graduated between one and ten years earlier. This high number of physicians who graduated recently may be due to the increase in the supply of undergraduate and postgraduate places at medical schools in Brazil.[11] This is indeed a limitation of this study: it was a cross-sectional survey; the number of doctors included who had graduated more than 20 years earlier was small; and the numbers of doctors in some specialties were also small. These factors made comparisons difficult. Moreover, another important limitation was the fact that the questionnaire asked for the name of the professional, thus reducing anonymity, which may have made the responses less trustworthy.

This study revealed that these professionals "usually" or "almost always" were the ones to transmit bad news (60% of the cases). This was similar to what was found by Lench, who observed this in 65% of the cases.[11] Regarding the concept of bad news, there was no significant divergence among the participants of the present study.

The SPIKES protocol envisages six steps in reporting bad news. The first step is the setting (S), i.e. the scenario, and this refers to doctors' preparation and the space within which they will deliver the news. The protocol states that a private place in which there will not be any interruptions should preferably be chosen. Moreover, it needs to be ascertained whether the patient wants to be accompanied or not during the conversation. The doctor should preferably be seated next to the patient, in order to offer him/her comfort and safety, as well as showing that both are at the same level and in the same situation. It is a time to appear calm and serene and to give the patient a moment of silence to listen.[16] These items can be analyzed through some questions in the questionnaire relating to how to give bad news (seeking a cozy private place, informing the patient while sitting at his/her bedside and listening carefully to the patient without interruptions). Most of the clinical staff in the present study said that they looked for a private environment (a specific room or an available office) in which to report the bad news, and a minority was also concerned with the comfort and coziness of the space. These findings are similar to the data of the

Table 4. Relationship between length of time since graduation and issues explored during the conversation

Length of time since graduation / Issues explored	1 to 10 years	11 to 20 years	More than 20 years
What patients already knew	51.65%	75%	66.67%
What patients wanted to know	42.00%	70.83%	100%
What patients' concerns were	63.74%	75%	50%

study by Martín Hernández and Trujillo Matienzo, in which the majority of the participants also worried about privacy.[13] Regarding the length of time since graduation, consistency with regard to seeking privacy was found. However, regarding quality, those who had graduated longer ago were more concerned about this, which could be explained by their greater experience.

The second step of the protocol is perception (P). This is the moment to check what the patient is aware of regarding his/her state of illness or condition, and to discover whether he/she would like to be informed about the condition and what his/her concerns are.[16] Questions relating to the issues explored in the conversation need to be analyzed. It was found in the present study that around half of the professionals did not address all of the issues, thus showing that there was a deficiency in the dialogue between doctors and patients. This contrasts with a study conducted in Cuba in 2009, in which these issues were better approached and explored by the doctors (around 72%).[13] This might be explained by lack of preparation among the professionals in our institution. It may also have been because the professionals' fears were mostly based on the patients' reactions and the possibility of taking away their hopes. Regarding the issues explored, none of the specialties was considered to be different from the others. Nevertheless, in relation to the length of time since graduation, these issues were covered more by the professionals who graduated more than 20 years earlier, which suggests that experience is essential in approaching patients regarding their health conditions.

The third step is the invitation (I). This is the time at which the degree of knowledge that patients want to have regarding their condition needs to be ascertained, while leaving time for the patient and/or family to ask questions.[16] At this point, the percentage of physicians who provided this opening for dialogue with their patients was analyzed. Only half of the professionals (among whom most had graduated more than 20 years earlier), confirmed that they offered this moment to their patients. This finding was not too different from what was reported in the study by Martín Hernández and Trujillo Matienzo, who found that this moment was offered only by 69% of the professionals.[13] In conclusion, a failing among the clinical staff was clearly noticeable, given that this attitude is important for the purpose of this step. However, the doctors may have had difficulty in implementing this because of their own fears regarding giving bad news. At this point, another deficiency among most doctors can be observed, given that they do not offer this essential moment to their patients, even though receiving bad news is a moment of anguish and discomfort.[16]

The fourth step, of knowledge (K), is the moment before and during communication of bad news. At this moment, the patient has been prepared and is expecting that bad news will be announced. Clear verbal and non-verbal language needs to be used, and technical jargon needs to be avoided. The information needs to be given gradually, so as to make sure that the patient understood everything.[16] In the present study, 84.3% of the doctors used both verbal and non-verbal language to talk with their patients. These results were far superior to the ones found in a study conducted in 2009, in which this proportion was only 40.9%.[13] However, it was reported in that study that this occurred because many of the professionals did not consider gestures and facial expressions to be non-verbal language, or were not even aware that they were using it. To avoid this bias during the interviews that we conducted in our university hospital, we explained and exemplified what non-verbal language would consist of. In relation to the length of time since graduation, there was much divergence, although most of the doctors used both verbal and non-verbal language. The majority of the professionals informed their patients according to their demands or those of family members. There was a discrepancy in relation to a study conducted in Cuba, in which despite the authors' opinion that the communication should be performed in a slow, gradual and continuous manner, 41.8% of the professionals did not do this. In relation to use of clear, understandable language and detailed explanations, the present study corroborates the findings from Cuba, given that the percentages were similar (such that clear and understandable language was used in 85.95% and 95.9% of the cases respectively and detailed explanations in 33.88% and 33.7% respectively).[13] In this regard, both of these studies endorse this step of the protocol, and differ only in details, which need to be better addressed by both studies.

The fifth step, of empathy (E), is the moment for doctors to show their patients that they have established a relationship of trust with them, and that they understand their patients' feelings and are compassionate to the situation.[16] Meanwhile, doctors should not take away patients' hopes, or feed them false hopes, although some professionals were seen to have done this. This is the moment when doctors should show their patients support in several ways, especially emotionally and spiritually. After all, when patients and their families receive bad news, this arouses feelings, emotions and concerns. Regarding emotional and spiritual support, the data from the present study resembled the findings of the 2009 study (90.08% and 74.38%), thus showing that support was provided for both patients and their families.[13] However, a very small number of the professionals in the present study provided false hope for their patients. These doctors had all graduated less than 10 years earlier. About one-third of the professionals established a relationship of trust with their patients and displayed empathy. In relation to establishing a relationship, the data differed completely from the findings in Cuba, where more than half of the doctors established a relationship of trust with their patients. On the other hand, in relation to empathy, the data were similar.[13] This may have occurred through lack of understanding of the term "put yourself in the patient's shoes", which required

the doctor to be empathetic and understand the patient's feelings and reactions. It could even be explained as reported by the author of the 2009 study, i.e. that offering trust and empathy to patients is not an easy task, even though it is important.[13] After all, giving bad news is a stressful situation for both patient and doctor, and therefore those who can avoid it always will.[8]

The sixth and final step is strategy and summary (S). This is the moment to ascertain whether the patient has understood all the information and perform a brief retrospective analysis, as well as presenting and discussing a therapeutic plan and prognosis for the illness, with the patient.[16] Therefore, as in the 2009 study, the participants preferred to talk firstly to the family and afterwards to the patient. Independent of the length of time since graduation, the majority of the professionals adopted this position. Consequently, it can be inferred that doctors are not prepared to talk about prognoses and treatments with their patients, since they delegate an attribution that should be part of the doctor-patient relationship, to family members.[13]

None of the participants was aware of any instrument or protocol that could help in addressing patients when bad news needs to be communicated. This result corroborates the findings of Lench and Destefani, who showed that 60% of the participants in their study were unaware of the SPIKES protocol. The longer the time since graduation was, the less was known about this subject.[11] Thus, the participants had learned through observing other specialists. The vast majority believed that adding the subject of how to give bad news to the undergraduate curriculum was important or very important, given that as shown by Lench, 69% of the participants had had no training on this subject and 60% considered that they had had a poor learning experience on this subject.[11] Therefore, the skills relating to giving bad news need to be improved. This medical skill can be improved through using a protocol as a guide for transmitting bad news, as well as through inclusion of "how to give bad news" in undergraduate courses. One proposed approach for such inclusion consists of teaching communication skills through dramatization and studying medical ethics and bioethics.[17,18]

FINAL REMARKS

From the results obtained, it can be concluded that many doctors have not developed sufficient skills relating to conveying bad news, since the crucial basic points of empathy and a good relationship of trust between doctors and their patients have not been well explored and worked out. In addition, professionals seem to be afraid to address certain issues among their patients (i.e. what patients already know and what they want to know about their health conditions). However, emotional, spiritual, informational and instrumental support is generally provided to both patients and their families. This is very important, given that bad news not only affects patients, but also their families.

In relation to the specialties, no conclusion can be reached regarding which of them are best prepared for the task of breaking bad news. However, regarding the length of time since graduation, we can conclude that in general, doctors with more than 10 years of experience since graduation, and especially those with more than 20 years of experience since graduation, were better qualified to provide bad news.

CONCLUSIONS

Methods for improving communication of bad news have been proposed and may be applied in medical practice in order to complement the course and improve medical skills.

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Annex 1. Original questionnaire answered by the physicians

QUESTIONÁRIO

Identificação

1) Nome:
2) Idade:
3) Especialidade
   a) Clínico Geral
   b) Cirurgião
   c) Nefrologista
   d) Cardiologista
   e) Endocrinologista
   f) Pneumologista
   g) Urologista
   h) Pediatra
   i) R1
   j) R2
   k) R3
   l) Outra?_____
4) Setor em que trabalha prioritariamente.
   a) UTI
   b) Ambulatório
   c) Bloco Cirúrgico
   d) Enfermaria
   e) Pronto Atendimento
   f) Outro?_____
5) Quanto tempo tem de formado?
   a) 1 a 10 anos
   b) 10 a 20 anos
   c) 20 a 40 anos
   d) Mais de 40 anos

Comunicando a má notícia:

1) O que é má notícia?
   a) Toda informação que acarrete em prejuízo físico do paciente.
   b) Apenas dar notícia de óbito.
   c) Qualquer informação transmitida que implique alguma alteração negativa e seria capaz de afetar a visão de vida do indivíduo ou suas perspectivas quanto ao futuro
2) Com que frequência dá más notícias?
   a) Quase sempre
   b) Muito
   c) Ocasionalmente
   d) Pouco
   e) Nunca
3) De que forma dá más notícias?
   a) Apenas de forma verbal
   b) Forma verbal e não verbal (toque, olhar, empatia...)
4) Como considera sua capacidade em dar más notícias?
   a) Muito boa
   b) Boa
   c) Aceitável
   d) Ruim
5) Onde você dá más notícias?
   a) Busca um local privado e aconchegante
   b) Informa em um consultório disponível
   c) Informa de maneira informal no corredor ou algum outro lugar fora do consultório
6) Se o paciente estiver acamado, você:
   a) Informa sentado ao lado da cama quando o paciente está acamado
   b) Informa parado ao lado cama quando o paciente está acamado
7) De que maneira fornece a má notícias? (pode ter mais de uma resposta)
   a) Com uma linguagem clara, compreensível, evitando palavras técnicas
   b) Explico com detalhes

Annex 1. Continues...

c) Dou esperanças mesmo que elas não existam
d) Estabeleço uma relação de confiança
e) Explico de maneira detalhada e técnica
f) Me ponho no lugar do paciente
g) Esclareço dúvidas

8) Ao dar a má notícia, você sempre diz a verdade sobre o diagnóstico, prognóstico e tratamento?
a) Nunca.
b) Evita dizer a verdade.
c) Fala tudo de uma vez só.
d) Dá de maneira cautelosa, cuidadosa, segundo demanda do paciente e ou familiares.

9) Para quem você conta a verdade?
a) Só ao paciente
b) Só à família
c) Ao paciente e ao seu acompanhante, ao mesmo tempo
d) Preferencialmente, primeiro ao paciente, depois à família
e) Preferencialmente, primeiro à família, depois ao paciente

10) Quando o paciente fala e/ou faz uma pergunta, você...: (pode ter mais de uma resposta)
a) Escuta atentamente e sem interromper o paciente
b) Escuta o que o paciente fala, mas interrompe sempre que tem algo para acrescentar
c) Não deixa que o paciente fale muito e é objetivo
d) Sempre dedica tempo para responder as suas perguntas

11) Quais conteúdos explora durante a conversa com o paciente (pode ter mais de uma resposta)?
a) O que o paciente sabe sobre sua condição de saúde
b) O que o paciente quer saber
c) O que preocupa o paciente
d) Apenas informa, não dando espaço para o paciente falar

12) Como você se sente ao dar uma má notícia?
a) Triste
b) Com pena
c) Sentimento de dever cumprido
d) Aliviado
e) Inseguro
f) Com medo

13) Quais medos você possui ao dar uma má notícia? (pode ter mais de uma resposta)?
a) Medo de ser culpabilizado
b) Medo de acabar com a esperança do paciente
c) Medo da morte e da doença propriamente dita
d) Medo de suas próprias reações emocionais
e) Medo das reações do paciente

14) A quem você fornece seu apoio:
14.1) Intrumental: a) Família b) Paciente c) Ambos
14.2) Informacional: a) Família b) Paciente c) Ambos
14.3) Emocional: a) Família b) Paciente c) Ambos
14.4) Espiritual: a) Família b) Paciente c) Ambos

15) Como aprendeu a dar más notícias?
a) Durante a graduação
b) Por método de tentativa e erro
c) Curso específico
d) Vendo outros especialistas
e) Outros_____

16) Você conhece algum instrumento que auxilie na habilidade de contar más notícias?
a) Sim
b) Não
Qual?_____

17) Quão importante acredita ser a incorporação de "Como dar más notícias" no curso de graduação?
a) Muito importante
b) Mais ou menos importante
c) Importante
d) Pouco importante
e) Sem importância

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Analysis of quality of life among asthmatic individuals with obesity and its relationship with pulmonary function: cross-sectional study

Análise da qualidade de vida de indivíduos asmáticos obesos e sua relação com a função pulmonar: estudo transversal

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KEY WORDS:
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Asthma.
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Respiratory function tests.
Spirometry.

PALAVRAS-CHAVE:
Obesidade.
Asma.
Qualidade de vida.
Testes de função respiratória.
Espirometria.

ABSTRACT

CONTEXT AND OBJECTIVE: The combined effect of obesity and asthma may lead to significant impairment of quality of life (QOL). The aim here was to evaluate the prevalence of asthma among obese individuals, characterize the severity of impairment of quality of life and measure its relationship with pulmonary function.

DESIGN AND SETTING: Observational cross-sectional study in public university hospital.

METHODS: Morbidly obese individuals (body mass index > 40 kg/m^2) seen in a bariatric surgery outpatient clinic and diagnosed with asthma, were included. Anthropometric data were collected, the Standardized Asthma Quality of Life Questionnaire (AQLQ(S)) was applied and spirometry was performed. The subjects were divided into two groups based on the median of the score in the questionnaire (worse < 4 and better ≥ 4) and were compared regarding anthropometric data and pulmonary function.

RESULTS: Among the 4791 individuals evaluated, 219 were asthmatic; the prevalence of asthma was 4.57%. Of these, 91 individuals were called to start multidisciplinary follow-up during the study period, of whom 82 answered the questionnaire. The median score in the AQLQ(S) was 3.96 points and, thus, the individuals were classified as having moderate impairment of their overall QOL. When divided according to better or worse QOL, there was a statistically difference in forced expiratory flow (FEF) 25-75%, with higher values in the better QOL group.

CONCLUSION: The prevalence of asthma was 4.57% and QOL was impaired among the asthmatic obese individuals. The worst QOL domain related to environmental stimuli and the best QOL domain to limitations of the activities. Worse QOL was correlated with poorer values for FEF 25-75%.

RESUMO

CONTEXTO E OBJETIVO: O efeito combinado de obesidade e asma pode levar a um comprometimento significativo da qualidade de vida (QV). O objetivo foi avaliar a prevalência de asma entre obesos, caracterizar a gravidade do comprometimento da QV e verificar sua relação com a função pulmonar.

TIPO DE ESTUDO E LOCAL: Estudo transversal observacional em hospital universitário público.

MÉTODOS: Foram incluídos indivíduos obesos mórbidos (indice de massa corporal > 40 kg/m^2), acompanhados num ambulatório de cirurgia bariátrica e diagnosticados com asma. Foram coletados dados antropométricos e aplicado o Standardized Asthma Quality of Life Questionnaire (AQLQ (S)), bem como a espirometria. Os indivíduos foram divididos em dois grupos com base na mediana obtida no escore do questionário (pior < 4 e melhor ≥ 4) e os grupos foram comparados aos dados antropométricos e função pulmonar.

RESULTADOS: Dos 4.791 indivíduos avaliados, 219 eram asmáticos; a prevalência de asma foi de 4,57%. Destes, 91 indivíduos foram chamados para iniciar o acompanhamento multidisciplinar no período do estudo, sendo que 82 responderam ao questionário. A pontuação mediana do AQLQ (S) foi de 3,96 pontos, portanto, classificados com prejuízo moderado na QV global. Quando divididos por melhor ou pior QV, houve diferença estatística no fluxo expiratório forçado (FEF) 25-75%, com maior valor no grupo com melhor QV.

CONCLUSÃO: A prevalência da asma na população estudada foi de 4,57% e há prejuízos na QV de obesos asmáticos, sendo o pior domínio de QV relacionado aos estímulos ambientais e o melhor domínio de QV relacionado às limitações das atividades. A pior QV se relacionou a piores valores de FEF 25-75%.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways that is associated with hyper-responsivity. It leads to recurrent episodes of wheezing, dyspnea, sensation of chest tightness and coughing, particularly at night or in the early morning. The obstruction to the airflow may be reversed spontaneously or by means of treatment. About 300 million individuals worldwide present asthma. The factors associated with the disease include environmental factors relating to allergies, occupation, smoking, infections, pollution and diet; and endogenous factors relating to genetics, gender and obesity.[1]

Asthma is diagnosed based on the symptoms and is confirmed through pulmonary function tests, such as spirometry and expiratory flow peak measurement. These enable evaluation of the severity of the limitation to the airflow and its reversibility and variability.[1]

In a meta-analysis by Beuther et al.,[2] it was observed that obese individuals were more likely to develop asthma than were lean individuals. The exact mechanism for development of asthma is uncertain, but the inflammation mediators produced by the adipose tissue may contribute towards a low-grade systemic inflammatory state and promote changes to pulmonary function, thus leading to episodes of bronchospasm.

Today, obesity has reached epidemic levels and has become a public health concern. In 2014, more than 1.9 billion adult individuals (39%) were at least overweight, and of these, more than 600 million were obese.[3] Obesity is defined as body mass index (BMI) greater than or equal to 30 kg/m^2 and considered to be a multifactorial disease.[4] Its probable causes are a combination of genetic, endocrine, behavioral, socioeconomic, psychological and environmental imbalances, and it leads to several comorbidities.[5]

Follow-up for asthmatic patients is necessary, with the aims of controlling the condition and avoiding exacerbations and the need for in-hospital assistance, especially when it is associated with obesity. Assessment of this information by means of questionnaires is useful within clinical practice and scientific research, since this allows standardization and reproducibility of measurements at low cost.

OBJECTIVE

The aims of this study were to evaluate the prevalence of asthma in the obese population, characterize its severity of impairment of the quality of life of asthmatic obese individuals and measure its influence on pulmonary function.

METHODS

Study design and setting

This was an observational cross-sectional study conducted at the bariatric surgery outpatient clinic of our university's teaching hospital. It was submitted for evaluation and was then approved by the local ethics review board (289.425). The laws and norms regarding studies on humans were followed, in accordance with resolution 196/96 of the National Health Council and all the participants in the study signed an informed consent statement.

Sampling and participants

The power of the sample was calculated based on the global AQLQ(S) (Standardized Asthma Quality of Life Questionnaire) and a sample power of 88% was obtained.

The inclusion criteria were that the subjects needed to:

- present morbid obesity (BMI ≥ 40 kg/m^2);
- be candidates for bariatric surgery;
- have a clinical diagnosis of asthma in accordance with the Global Initiative for Asthma consensus statement[1] and/or antecedents of any episode of bronchospasm at any time during their lives and/or current or previous use of medication to treat asthma.

The exclusion criteria were the presence of:

- smoking habit;
- cognitive impairment that could impede performance of the clinical tests and completion of the questionnaire;
- respiratory diseases other than asthma;
- congestive heart failure or cardiovascular ischemic disease.

The recruitment period for the participants was from February 2015 to April 2016.

Adult individuals were screened at the time of registration to enter the outpatient clinic and become candidates for bariatric surgery. On this occasion, they filled out a registration form that asked for information about the presence of asthma. Those who reported having asthma or experiencing episodes of bronchospasm without an ultimate diagnosis, and who fulfilled the other criteria, were then informed about the procedures of the study and were invited to take part in it. The procedures would involve clinical confirmation of the diagnosis of asthma by means of consultations with a physiotherapist, evaluation with a pneumologist physician and performance of spirometry.

Pulmonary function tests and asthma diagnosis

Asthma was investigated based on the symptoms that individuals reported having had over their whole lifetime, such as episodes of bronchospasm, breathlessness, sensation of chest tightness and coughing,[1,6] or in situations in which individuals were routinely using medications for asthma, in accordance with the Global Initiative for Asthma consensus statement.[1] Once diagnosed, these individuals would undergo pulmonary function tests to assess the severity of the disease. Other respiratory diseases were excluded based on anamnesis and pulmonary function test.

Spirometry was performed at the Pulmonary Function Laboratory under supervision by a technical team and the norms of the American Thoracic Society (ATS) and European Respiratory

Society (ERS)[7] were followed. To evaluate measurements of pulmonary volumes and flows, two maneuvers were performed: slow vital capacity and forced vital capacity. The maneuvers were performed repeatedly until three acceptable curves were obtained, of which two needed to be reproducible. The total number of trials could not exceed eight. The subjects rested for 10 minutes before the test and received appropriate orientations during the test.

The maneuvers were performed at two times: before and after using a bronchodilator (salbutamol, 200-400 μg) to observe the increase in the forced expiratory volume in the first second (FEV_1) and/or the peak expiratory flow (PEF). Asthma is diagnosed when there is a 12% or 200 ml increase in FEV_1 and a 20% or 60 liter/min increase in PEF, in relation to the pre-bronchodilator values. The subjects were instructed to suspend their use of bronchodilator for 8-12 hours before the test.[1,6]

Evaluation procedures and outcome measurements

Antropometric data were collected and the quality of life was assessed follows.

The following anthropometric data were collected: weight, height and BMI. Weight was measured by means of a digital weighing machine (Filizola ID-1500, Brazil), with a capacity of 300 kg capacity and precision of 0.1 kg. Height was measured by means of a wall-mounted stadiometer, with a capacity of 2 meters and precision of 0.1 cm. Body mass index (BMI) was calculated by means of Quetelet's formula,[8] i.e. weight/(height^2).

Quality of life was assessed by means of the Standardized Asthma Quality of Life Questionnaire (AQLQ(S)), which is a self-applicable questionnaire consisting of 32 questions that evaluate the last two weeks within four separate domains (impairment of activities, symptoms, emotions and environmental stimuli). It was developed by Juniper et al.[9] and was validated and standardized by Juniper et al.[10] It has been translated into Portuguese for use in Brazil, as well as into more than 30 other languages. The Brazilian Portuguese version was validated and was considered to have good reproducibility and characteristics similar to those of the original instrument.[11] Thus, it could be used for the population of the present study.

The questionnaire scores are calculated from the means of each domain; the scores range from 1 to 7. The higher the score is, the better the quality of life is. The questionnaire contains specific questions relating to asthma and respiratory symptoms that are triggered in specific activities and, therefore, assesses these conditions without connection with obesity.

Statistical analysis

The data were encoded for the SPSS 13.0 software and descriptive analysis was performed. The individuals were divided into two groups based on the scores obtained from the questionnaire (better or worse quality of life). The cutoff value for defining the groups was obtained through descriptive analysis on the overall AQLQ(S), which found a median score of 3.96 points. Thus, the cutoff value of 4 was used. In addition, according to Juniper et al.,[9] 4.0 is an intermediate score in the questionnaire and therefore separates between worse and better quality of life.

In this manner, the subjects were then divided between group 1 (worse QOL; score < 4) and group 2 (better QOL; score ≥ 4). These groups were compared regarding their anthropometric data and pulmonary function results, by means of the Mann-Whitney test. The significance level used was 5% (P-value < 0.05).

RESULTS

During the study period, there were three inscription events to enlist candidates for bariatric surgery at our service. On the first occasion (March 2014), 1,782 individuals were registered and, of these, 82 (4.6%) were reported as asthmatic; on the second occasion (December 2014), 1,781 were registered and, of these, 61 (3.42%) were reported as asthmatic; and on the third occasion (November, 2015), 1,228 individuals were registered and, of these, 76 (6.18%) were reported as asthmatic. Hence, out of an overall population of 4,791 individuals with obesity, 219 (5.57%) reported having asthma symptoms. **Figure 1** shows a graphic representation of this phase of the recruitment.

For patients to be called up to begin the preoperative program, the criteria used were their severity of obesity and comorbidities, their position on the waiting list and the availability of preoperative examinations and surgical vacancies. Up to the end of the study period, 91 asthmatic individuals were called up to enter the program and, of these, 82 adequately filled out the proposed questionnaire. All the individuals in our sample who reported in this file that they had suggestive symptoms and who were called up for the program were confirmed as having a clinical diagnosis of asthma.

Anthropometric data were collected from these 82 individuals and are presented in **Table 1**. After analysis on the sample, they were stratified as having "better" or "worse" QOL, according to the scores obtained in the questionnaire. The features that significantly differed between the groups were height (P = 0.004) and pre-bronchodilator pulmonary function test values, which presented a significant difference regarding forced expiratory flow (FEF) 25-75%, which was higher in the group with better QOL group (P = 0.043). **Table 2** shows the characteristics of both groups.

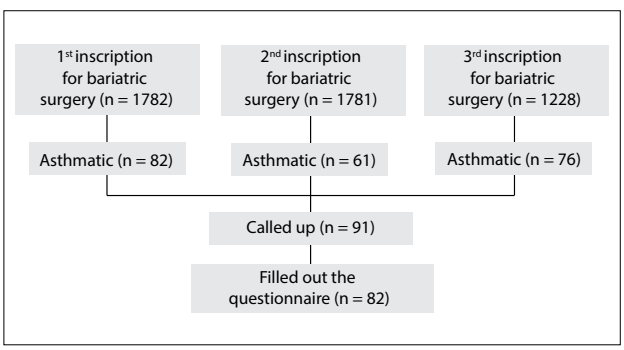

Figure 1. Patient recruitment flow in the study.

Table 1. Overall characteristics of the study population. Data expressed as means and standard deviations (SD), and as medians and quartiles

	n	Mean ± SD	Median	1st quartile	3rd quartile
Anthropometry					
Age (years)	81	39.24 ± 9.42	37.0	32.0	46.0
Weight (kg)	80	117.07 ± 18.62	115.3	103.9	125.8
Height (cm)	80	160.91 ± 6.00	161.5	157.0	165.0
BMI (kg/m^2)	80	45.27 ± 6.79	44.3	41.35	48.5
Excess weight (kg)	80	58.48 ± 17.65	56.25	46.15	65.57
AQLQ(S)					
Overall	82	3.87 ± 1.45	3.96	2.60	4.94
Limitation on activities	82	4.12 ± 1.38	4.13	2.79	5.36
Symptoms	82	3.89 ± 1.53	3.83	2.50	5.08
Emotions	82	3.71 ± 1.86	3.50	1.80	5.45
Environmental stimuli	82	3.30 ± 1.76	2.62	1.75	4.81
Pulmonary function					
FVC (L)	73	2.85 ± 0.62	2.87	2.37	3.30
FEV_1 (L)	73	2.24 ± 0.59	2.24	1.78	2.70
FEV_1/FVC (%)	73	77.17 ± 12.46	79.70	72.90	84.65
PEF (L/s)	73	5.30 ± 1.44	5.36	4.40	6.11
FEF 25-75 (L/s)	73	2.29 ± 1.12	2.12	1.47	3.05
FEF75 (L/s)	63	4.59 ± 1.70	4.65	3.51	5.85
FEF50 (L/s)	63	2.97 ± 1.42	2.89	1.87	4.05
FEF25 (L/s)	63	0.99 ± 0.54	0.81	0.59	1.36
FIVC (L)	73	2.85 ± 0.62	2.87	2.39	3.21
PIF (L/s)	73	4.16 ± 1.36	4.05	3.07	5.14

BMI = body mass index; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1st second; PEF = peak expiratory flow; FEF = forced expiratory flow; FIVC = forced inspiratory vital capacity; PIF = peak inspiratory flow; L = liter.

Table 2. Comparison of the pre-bronchodilator pulmonary function tests between the "better" and "worse" quality of life (QOL) groups (cutoff value = 4)

	Median (1st-3rd quartile)		P-value
	Worse QOL (n = 41)	Better QOL (n = 41)	
Anthropometry			
Age (years)	37.0 (32.0-45.5)	37.0 (31.2-46.0)	0.951
Weight (kg)	112.6 (103.9-120.7)	118.4 (103.9-131.4)	0.130
Height (cm)	159.0 (154.2-163.7)	163.0 (158.2-166)	0.004*
BMI (kg/m^2)	43.5 (40.4-49.2)	45.25 (41.6-47.8)	0.773
Excess weight (kg)	55.05 (45.0-63.8)	59.55 (46.6-71.1)	0.235
Pulmonary function			
FVC (L)	2.76 (2.31-3.16)	2.93 (2.54-3.38)	0.126
FEV_1 (L)	2.13 (1.52-2.59)	2.35 (1.91-2.86)	0.060
FEV_1/FVC (%)	77.55 (69.5-84.02)	82.10 (76.5-85.2)	0.103
PEF (L/s)	5.26 (3.98-6.11)	5.44 (4.49-6.11)	0.504
FEF 25-75 (L/s)	1.77 (1.11-2.87)	2.51 (1.74-3.35)	0.043*
FEF75 (L/s)	4.35 (2.70-5.85)	4.72 (3.98-5.69)	0.371
FEF50 (L/s)	2.62 (1.65-3.82)	3.50 (2.08-4.46)	0.105
FEF25 (L/s)	0.77 (0.45-1.28)	0.95 (0.61-1.36)	0.132
FIVC (L)	2.85 (2.19-3.13)	3.0 (2.55-3.38)	0.090
PIF (L/s)	4.06 (2.99-5.02)	4.01 (3.11-5.64)	0.982

*Statistically significant P value; BMI = body mass index; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1st second; PEF = peak expiratory flow; FEF = forced expiratory flow; FIVC = forced inspiratory vital capacity; PIF =: peak inspiratory flow; L = liter.

DISCUSSION

In a meta-analysis conducted by Beuther et al.,[2] obese individuals presented higher risk of developing asthma than did lean subjects. The prevalence of asthma in the present study was 4.57% in a population of 4,791 individuals. This prevalence is low in comparison with what was found in the study by Melo et al.,[12] which was 18.5% in a population of 363 obese individuals. However, in our study, asthma was reported in our subjects' registration files for their entry to the preoperative program for bariatric surgery, i.e. before contact with the multiprofessional team or detailed clinical interview.

It is known that asthma may be underdiagnosed in low-income obese populations for several reasons, such as poor access to information or to specific healthcare services that provide diagnosis and management of asthma. Moreover, individuals may interpret their own episodes of wheezing as physical tiredness caused by obesity, which would remit without use of medications or medical evaluation. In such situations, they might not provide this information at the time that the registration file is filled out. However, all the individuals in our sample who reported in this file that they had suggestive symptoms and who were called up for the program were confirmed as having a clinical diagnosis of asthma, determined through the reported clinical history.

All the individuals in this study present grade III obesity (BMI 40-49.9 kg/m^2), with a mean BMI of 45.27 ± 6.79 kg/m^2. Grade III obesity causes severe changes to pulmonary function due to several factors, such as fat deposition around the thorax and abdomen, which limits adequate movements of the thorax[13] and changes pulmonary compliance.[14,15] This leads to microatelectasis in the pulmonary inferior lobes[16,17] and reduces functional capacity,[13,18] which compromises performance of simple daily activities, due to early tiredness. Furthermore, the low-grade systemic inflammatory state caused by fat tissue has the capacity to influence the lung parenchyma,[19] thereby leading to episodes of bronchospasm.

Besides changes to pulmonary function, obesity may lead to physical limitations, postural changes and joint overload,[20] which gives rise to joint pain and impairment of walking ability and daily activities. Such impairments, both pulmonary and physical, directly affect the QOL of these individuals, and weight loss is strongly recommended. Hence, the individuals called up for the study were instructed to begin preparations for the preoperative assessment for bariatric surgery, which favors a healthy lifestyle, especially regarding diet and physical activity.

The QOL data obtained demonstrated that the individuals scored in the medium band of the score scale from 1-7 (median = 3.96 points) and, thus, presented moderately compromised QOL in all the domains evaluated. The domain with the best final score related to limitations on activities (median = 4.13 points) and the worst related to environmental stimuli (median = 2.62 points).

The domain with the best score (albeit still denoting moderate impairment), relating to limitations on activities, comprised questions on specific daily activities that may cause episodes of bronchospasm and breathlessness and the degree of limitation that these cause to the individual (such as walking, running, practicing exercises, working, socializing etc.). These were not necessarily physical limitations, but could also be limitations relating to fear of exposure to risky situations.

The worst-scoring domain related to environmental stimuli, which comprised specific questions on symptoms caused by smoke, dust, foul weather, pollution and perfume fragrances. External environmental stimuli may potentiate systemic pulmonary inflammation, thus leading to hyperresponsivity of the airways and episodes of bronchospasm.

When the individuals were stratified into two groups according to their asthma-related QOL, it was observed that the individuals with better QOL also presented significantly higher FEF 25-75% (P = 0.043). FEF represents the mean forced expiratory flow in the intermediate band of forced vital capacity (FVC), i.e. between 25 and 75% of the FVC curve.[21] FEF 25-75% depends on the elastic retraction force of the lungs, the permeability of the small airways and the muscle strength. Its measurement provides information on the permeability of the small airways and is unrelated to the patient's collaboration.[22] Thus, all of the mechanical and inflammatory changes present in the lungs of morbidly obese individuals may lead to changes in the permeability of low-caliber airways, which is mirrored in measurements of FEF 25-75%.[12]

Although the FEV_1/FVC% ratio is the measurement that best represents obstructive disorders,[21] it was normal in our study, albeit at the lower limit. According to Pereira,[21] patients with established chronic obstructive pulmonary disease (COPD) tend to show much more surprising changes in FEF 25-75% than in the FEV_1/FVC% ratio. However, because of the correlation between FEF 25-75% and FEV_1/FVC%, the FEF 25-75% measurement becomes redundant when the FEV_1/FVC% ratio is abnormal. Therefore, if the FEV_1/FVC ratio is borderline, a reduction in FEF 25-75% or other terminal flows indicates airflow obstruction in individuals with symptomatic respiratory disorders.

According to Lebecque et al.,[22] for mild asthma, FEF 25-75% appeared to be more sensitive than the FEV_1/FVC ratio for indicating the presence of small-caliber airway obstruction.

In the present study, although no relationship was found for other spirometric variables, it could be seen that the values of FEV_1, FEF and FEF 25% also were below the normal range when the non-stratified sample was analyzed, this finding is expected in asthmatic individuals.[21,23]

Some studies in which pulmonary function tests were performed on obese individuals without pulmonary abnormalities showed significant reductions in functional residual capacity (FRC)[13,24] and expiratory reserve volume (ERV)[13,25,26] that were attributable to the mechanical changes that fat tissue causes to the thorax. Nonetheless, the changes in FEF 25-75% was attributed by Sood[13] to inflammatory

changes that occurred in the lungs of obese individuals, thereby leading to premature closure of the small airways during forced expiration. This might explain the relationship between the severity of asthma and the observed values of FEF 25-75%. Such changes in the small airways may contribute towards situations in which low effort or low environmental stimuli provoke episodes of bronchospasm and breathlessness, thus compromising the QOL of these individuals.

There is recent evidence highlighting the burdens on QOL caused by certain situations, such as asthma. In a study that used the same QOL evaluation questionnaire as in the present study, Rocha[27] observed that asthma had a significant impact on QOL even when partly controlled. Furthermore, in a review of literature conducted by Araújo et al.,[28] it was concluded that the QOL and sleep quality of asthmatic individuals were compromised. On the other hand, in a study by Pereira et al.[29] that used the Saint George's Respiratory Questionnaire (SGRQ) to assess the QOL of individuals with asthma and chronic obstructive pulmonary disease (COPD), it was observed that, when the disease was classified as mild to moderate and was adequately treated, there was no impairment of QOL.

In studies that evaluated the impact of obesity on QOL, there was evidence that obesity led to impairment of QOL. Weight loss might improve the overall QOL within this group.[30-32]

Hence, since impairments of QOL occur in both diseases, an association between them would be expected to cause even more damage. This explains the importance of measuring QOL in these cases, in such a way that therapeutic strategies and goals can be designed.

Since we identified that worse QOL in the present study was related to greater impairment of pulmonary function, it is possible for the attending physician to identify individuals with disease of greater severity by means of a simple questionnaire that may be self-applicable. This would reduce the need for additional pulmonary function tests and, thus, minimize the cost of therapy for these individuals, since improvement of the symptoms and QOL should be the ultimate goal.

Therefore, the possibility of classifying the QOL of asthmatic obese individuals by means of a questionnaire may provide attending physicians with significant information on the degree of impairment of pulmonary function in these individuals and make it possible to define strategies for better and individualized therapy.

Limitations

Although the Brazilian Portuguese version of the questionnaire has many properties similar to the original instrument, and is a valid instrument for this population according to the authors who validated it, these authors mentioned in their validation study that hardly any study can claim to provide full validation. Therefore, studies that validate the questionnaire more appropriately would be required, and this might constitute a form of bias for research that uses the instrument. Nonetheless, the original questionnaire was translated into Brazilian Portuguese in accordance the internationally accepted methodology.

CONCLUSION

The prevalence of asthma in the study population was 4.57%. The QOL of individuals with asthma and obesity was impaired. The worst QOL domain related to environmental stimuli and the best QOL domain related to the limitations of the activities. Worse QOL correlated with lower values for FEF 25-75% in the pulmonary function test.

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Quality of diet plans for weight loss featured in women's magazines. A cross-sectional descriptive study

Qualidade de planos dietéticos para perda de peso veiculados em revistas femininas. Um estudo descritivo transversal

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KEY WORDS:
Nutritive value.
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Weight loss.
Publications.
Female.

PALAVRAS-CHAVE:
Valor nutritivo.
Dieta.
Perda de peso.
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Feminino.

ABSTRACT

CONTEXT AND OBJECTIVE: Brazil has the fifth largest population of obese individuals in the world. Women's magazines publish a large number of diet plans, and therefore the objective of this study was to assess the quality of these plans.

DESIGN: Cross-sectional descriptive study.

METHODS: We included the Brazilian women's magazines of highest circulation published between January and June 2014 that advertised diets for weight loss on their covers. We extracted the quantities of macro and micronutrients from each of these diet plans and compared these quantities with the World Health Organization nutritional guidelines for adult women. We also checked the total energy quantities of these plans, and any recommendations about water intake and physical activity.

RESULTS: We identified 136 potentially eligible magazine issues; 41 were excluded and 95 issues of 6 different magazines were included in the study. We found that 83.1% of the plans had carbohydrate and fiber levels below the recommendations. On the other hand, the protein and saturated fatty acid levels were above the recommendations in 97.8% and 95.7% of the plans, respectively; 75.7% of the diets had inadequate calcium levels and 70.5% had low iron levels. Only 30 plans specified the total daily quantity of dietary energy and in 53.3% of these, the information was inconsistent with our estimates; 20% of the plans had no recommendations on daily water intake and 37.5% did not give recommendations regarding physical activity practices.

CONCLUSION: The diet plans for weight loss featured in Brazilian women's magazines are of low quality.

RESUMO

CONTEXTO E OBJETIVO: O Brasil tem a quinta maior população de obesos do mundo. Revistas femininas publicam um grande número de planos dietéticos. Assim, o objetivo deste estudo foi avaliar a qualidade desses planos.

TIPO DE ESTUDO: Estudo descritivo transversal.

MÉTODOS: Incluímos as revistas femininas brasileiras de maior circulação publicadas entre janeiro e junho de 2014 que tivessem uma chamada de dieta para perda de peso em sua capa. De cada plano dietético, foi extraída a quantidade de macro e micronutrientes. Comparamos esses valores com as diretrizes nutricionais da Organização Mundial de Saúde para mulheres adultas. Verificamos também a quantidade total de energia, se o plano recomendava consumo de água e prática de atividade física.

RESULTADOS: Um total de 136 exemplares potencialmente elegíveis foi identificado; 41 foram excluídos e 95 exemplares de 6 revistas diferentes foram incluídos no estudo. A análise mostrou que 83,1% dos planos apresentaram valores de carboidratos e de fibras menores do que os recomendados. Por outro lado, o teor de proteína e de ácidos graxos saturados foi maior do que o recomendado em 97,8% e 95,7% dos planos, respectivamente, e 75,7% dos planos tinham teor inadequado de cálcio e 70,5% de ferro. Apenas 30 planos especificaram a quantidade total de energia diária e em 53,3% desses, a informação foi discordante com nossas estimativas; 20% dos planos não recomendavam consumo diário de água, 35,7% não recomendavam a prática de atividade física.

CONCLUSÃO: A qualidade dos planos dietéticos para perda de peso veiculados em revistas femininas brasileiras é baixa.

INTRODUCTION

There are currently 2.1 billion overweight individuals in the world, which represents a huge increase in relation to the 875 million overweight individuals in the 1980s. Estimates indicate that obesity and overweight caused 3.4 million deaths worldwide in 2010 and reduced life expectancy by 3.9% years.[1] Brazil is the country with the fifth largest number of obese individuals in the world, surpassed only by the United States, China, India and Russia.[1] In São Paulo, the largest city in Brazil, 18.2% of all women and 17.5% of all men are obese.[2] Emotional and genetic factors, along with an overall increase in dietary energy and a sedentary lifestyle, are the main causes of the increased prevalence of obesity.[3,4]

In parallel with the national increase in the prevalence of obesity, the last three decades stand out as a period during which body image and "being fit" became fundamental values within Brazilian culture. Nowadays, fitness and body image are highly prioritized and a large number of individuals regard any slight weight gain as a major problem. Many people whose weight is within the normal range feel that they are overweight. In this culture, simply accepting one's body shape is frowned upon since the body is always imperfect and in need of correction or transformation.[5-7]

Despite the many health consequences and the high economic costs of obesity, the search for an efficient diet for weight loss and maintenance is still ongoing. The World Health Organization (WHO) recommends that, in order to promote healthy and gradual weight loss, diet plans should limit dietary energy consumption and encourage physical activity.[8,9]

There is relentless pursuit of a fit body that conforms to the standards imposed by society, and constant surveillance of food intake according to recommended diet plans that produce a slow and steady weight loss. These coexist with an avalanche of popular diet plans that promise quick and easy ways to slim down. Most modern popular diets encourage reducing or excluding a specific macronutrient or excessive reduction of total dietary energy, and are only efficient over the short term.[10-12]

The media plays an important role in providing information about eating habits, nutrition, health and related matters, including diet plans and fitness programs.[12-14] Most women are exposed to all kinds of diet plans for weight loss in magazines, which also lead them to be intensely concerned about their weight, appearance and body image. Women of all sizes and shapes are motivated to lose weight because of fashion and not because of the health risks associated with being obese or overweight.[11] It is also increasingly common to find nutrition articles in popular magazines that include interviews with celebrities. When public figures (especially actors and athletes) give testimonials about their eating habits, these can have far-reaching and potentially harmful effects on the population because many readers tend to believe any information endorsed by role models.[15]

Professional nutritionists can and should also use these media channels to reduce the lack of information and confusion that lay people have about nutrition and to disseminate correct facts about adequate eating habits, to promote health. These educational efforts can also be very useful when working with group or individual nutritional counseling.[15-19]

In Brazil, women buy 60% of the popular magazines.[20] Many of these weekly or monthly issues publish a large number of diet plans of unknown quality. Therefore, it is important to assess the content and adequacy of these diet plans from a nutritional perspective. The results from the present study will help to inform the public about the potential harm and benefits of diet plans published in popular magazines.

OBJECTIVES

To assess the quality of diet plans for weight loss published in Brazilian women's magazines.

METHOD

This was a descriptive cross-sectional study conducted in the postgraduate program of the Federal University of São Paulo and approved by the Research Ethics Committee of the institution under the number 25223.

The analysis unit was diet plans for weight loss presented in articles published in popular women's magazines. The articles included in this study were obtained using a pre-specified sampling strategy. We selected the magazines with the highest circulation between January and June 2014 that were classified as addressing "feminine", "behavior and beauty" and "quality of life and health" matters, according to the 2014 Brazilian media data registry.[20,21] All of the issues of these magazines that advertised diets for weight loss on their covers were considered eligible for inclusion.

After reading each potentially eligible full-text article, in printed versions of the journals, we excluded those that did not provide a full diet plan (i.e. that did not allow us to extract the nutritional content of the plan), those that only provided general nutritional recommendations and those that proposed diet plans lasting less than 7 days.

We extracted data from all the eligible articles using a form specifically created for the study. Estimation of the total caloric values and nutritional composition of the diet plans of each article included was performed in duplicate by two independent investigators using the DIETPRÓ software, the database of the AVANUTRI software and the Brazilian Food Composition Table.[22]

We analyzed the adequacy of each plan suggested in the magazine articles by comparing the estimated nutritional macro and

micronutrient content of the diet plan with international nutritional recommendations for women between 19 and 50 years of age. For carbohydrates, proteins, fats and saturated fatty acids, we compared the diet plan content according to the latest WHO recommendations.[23] Briefly, these recommend that adults should get 55% to 75% of their total daily calories from carbohydrates, 15% to 30% from fats (less than 10% from saturated fatty acids) and 10% to 15% from proteins. We classified diet plans with less than 55% carbohydrates as being below the recommendations, those between 55% and 75% as adequate and those with more than 75% carbohydrates as above the recommendations. The fat content was categorized as low when it represented less than 15% of the total dietary energy, adequate when it was between 15% and 30% and high when it was more than 30%. Plans with saturated fatty acid values below 10% were considered adequate and above this were considered high. Plans in which the protein content accounted for between 10% and 15% of the total dietary energy were classified as being adequate; those below and above these figures were categorized as being below and above the recommendations, respectively.[23,24]

We assessed the fiber content of each diet according to the latest dietary reference intake (DRI) values proposed by the Institute of Medicine (IOM).[25] Diet plans with less than 25 g of fibers were categorized as having low fiber content and those with 25 g or more were considered adequate, since there is no upper reference level for fibers.

We analyzed the micronutrient content (calcium, iron, vitamin C and sodium) of the diet plan according to the IOM recommendations for vitamins and minerals.[26-29] For calcium, we used the micronutrient apparent adequacy criterion proposed by the DRI.[30] The formula used was: $Z = Y - EAR/\sqrt{Vnec + (Vint/n)}$, where Y = average intake of micronutrients obtained from food surveys, or in this case, the diet plans of women's magazines; EAR = estimated average requirement, i.e. mean micronutrient needs according to age and sex; Vnec = variance of needs, which corresponds to 10% of EAR = 0.1 x EAR; and Vint = intrapersonal variance, according to age and sex. Intrapersonal standard deviation (SD) was obtained.[30]

We analyzed the vitamin C and iron content, as suggested by the IOM subcommittee that published the DRI.[30,31] Values below the estimated average requirement (EAR), which is 60 mg for vitamin C and 8.1 mg for iron, were considered to be lower than the recommendations. Values between the EAR and the recommended dietary allowances (RDA), which are 75 mg and 18 mg for vitamin C and iron, respectively, were considered to represent a risk of inadequacy. Values between the RDA and the tolerable upper intake level (UL), which is 2000 mg for vitamin C and 45 mg for iron, were considered appropriate and values above the UL were considered to be higher than the recommendations.[30,31] For sodium, the adequate intake and UL values were used, since there is no EAR value for this mineral. Values between the adequate intake and UL were considered appropriate and values greater than the UL were considered to be higher than the recommendations.[28]

We also checked whether the article specified the total daily calorie content of the diet plan, and whether it recommended appropriate daily water intake and encouraged readers to practice physical activities along with the diet plan. We calculated the total daily calorie content of each plan and compared this with the values provided in the articles that presented this information. The total dietary energy of the diet plan was considered correct if it was between 90% and 110% of our calculations.[18,19,32] Finally, we checked whether the article cited the name of the professional responsible for elaboration of the plan.

The results are presented using descriptive statistics.

RESULTS

We identified a total of 53 different women's magazines (23 weekly and 30 monthly titles) on the website of the National Association of Magazine Editors. Six different women's magazines (five weekly and one monthly) were included in the study. The numbers of copies sold and types of the magazines were: 188,895 (A, weekly); 137,138 (B, weekly); 125,774 (C, weekly); 67,500 (D, weekly); 27,520 (E, weekly); and 209,772 (F, monthly). A total of 136 issues of these six magazines had diet plans on their covers and were selected for full-text reading; 41 were excluded for various reasons and 95 articles were included in the study (**Figure 1**).

The 95 articles included were published in the six different magazines as follows: 11 articles (11.5%) in magazine A; 21 (22.1%) in magazine B; 17 (17.8%) in magazine C; 25 (26.3%) in magazine D; 15 (15.7%) in magazine E; and 6 (6.3%) in magazine F.

Quantitative analysis on the content of the 95 diet plans revealed that 79 plans (83.1%) had carbohydrate levels and 93 (97.8%) had protein levels below those recommended by the reference used. On the other hand, 63 (66.3%) of the plans proposed adequate fat levels and 91 (95.7%) of the plans had saturated fatty acid levels above the recommendations (**Table 1**).

Seventy-nine (83.1%) of the plans had a fiber content lower than the recommendations, but 49 (51.5%) and 85 (89.4%) of the plans had adequate sodium and vitamin C levels, respectively. Sixty-seven (70.5%) of the plans were categorized as having an iron level that represented a risk of inadequacy (**Tables 2** and **3**). Finally, 72 (75.7%) of the plans had a 70% to 98% likelihood of inadequacy in relation to calcium.

Less than one third (n = 30; 31.5%) of the diet plans specified the total dietary energy expressed in calories. In 16 (53.3%) of these plans, the total informed by the magazine was discordant with our calculations: in 9 plans (56.2%), our calculation was more than 10% higher than the number specified in the magazine; and in 7 (43.75%),

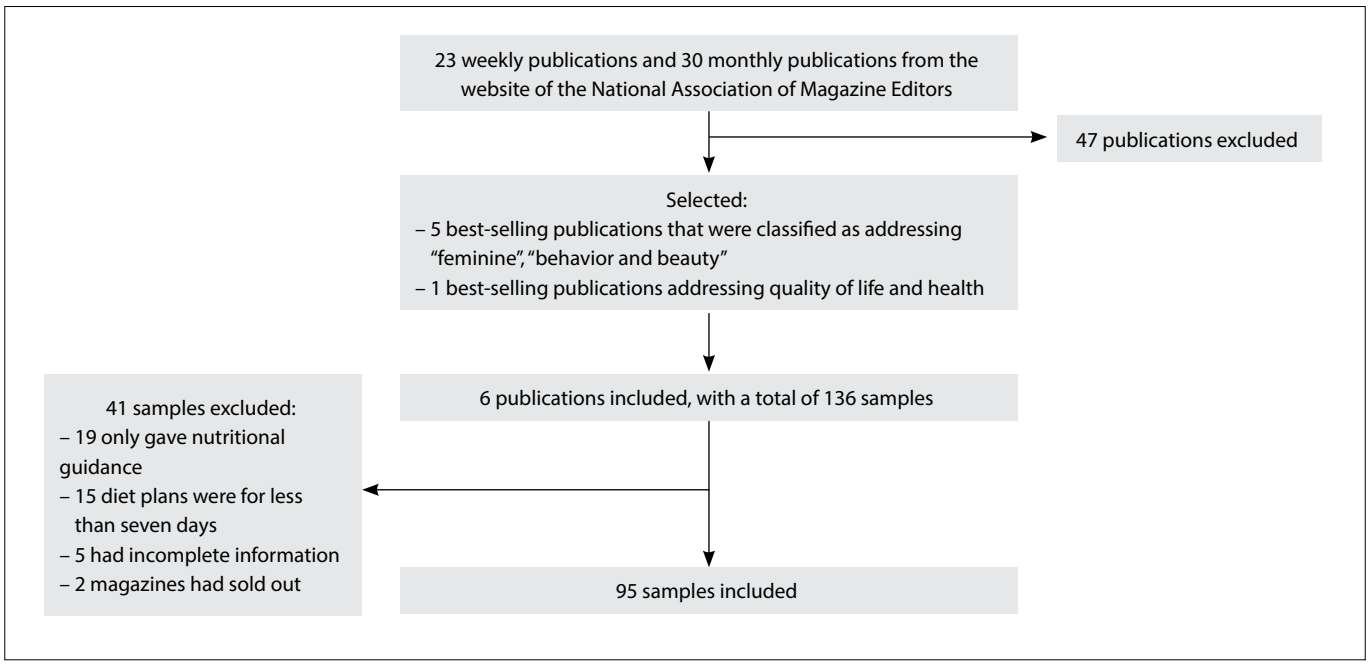

Figure 1. Flowchart of the sample acquisition: January-June 2014.

Table 1. Quantitative analysis on the adequacy of provision for carbohydrates, proteins, lipids and saturated fatty acids.

Publication	Below recommendation		In line with recommendation		Above recommendation		Total	
	n	%	n	%	n	%	n	%
Carbohydrates (%)								
Magazine A	11	100.0	0	0.0	0	0.0	11	
Magazine B	15	71.4	6	28.5	0	0.0	21	
Magazine C	14	82.3	3	17.6	0	0.0	17	
Magazine D	20	80.0	5	20.0	0	0.0	25	**100.0**
Magazine E	13	86.6	2	13.3	0	0.0	15	
Magazine F	6	100.0	0	0.0	0	0.0	6	
Total	**79**	**83.1**	**16**	**16.8**	**0**	**0.0**	**95**	
Proteins (%)								
Magazine A	0	0.0	0	0.0	11	100.0	11	
Magazine B	0	0.0	0	0.0	21	100.0	21	
Magazine C	0	0.0	1	5.8	16	94.1	17	
Magazine D	0	0.0	0	0.0	25	100.0	25	**100.0**
Magazine E	0	0.0	1	6.6	14	93.3	15	
Magazine F	0	0.0	0	0.0	6	100.0	6	
Total	**0**	**0.0**	**2**	**2.1**	**93**	**97.8**	**95**	
Lipids (%)								
Magazine A	0	0.0	7	63.6	4	36.3	11	
Magazine B	0	0.0	14	66.6	7	33.3	21	
Magazine C	1	5.8	10	58.8	6	35.2	17	
Magazine D	1	4.0	18	72.0	6	24.0	25	**100.0**
Magazine E	0	0.0	11	73.3	4	26.6	15	
Magazine F	0	0.0	3	50.0	3	50.0	6	
Total	**2**	**21.1**	**63**	**66.3**	**30**	**31.5**	**95**	
Saturated fatty acids (%)								
Magazine A	0	0.0	0	0.0	11	100.0	11	
Magazine B	0	0.0	1	4.7	20	95.2	21	
Magazine C	0	0.0	0	0.0	17	100.0	17	
Magazine D	0	0.0	1	4.0	24	96.0	25	**100.0**
Magazine E	0	0.0	2	13.3	13	86.6	15	
Magazine F	0	0.0	0	0.0	6	100.0	6	
Total	**0**	**0.0**	**4**	**4.2**	**91**	**95.7**	**95**	

our calculation was more than 10% lower than this number. Only 19 (20%) of the articles provided information on the daily water intake.

Approximately one third (n = 34; 35.7%) of the articles encouraged readers to increase their level of physical activity along with the diet for weight loss.

Almost all (n = 92; 96.8%) of the articles stated the name of the professional responsible for elaborating the diet plan or who provided advice or comments about it. In most cases (n = 84; 88.4%), this professional was a nutritionist; in 6 articles (6.3%), a physician was named, and in 2 (2.1%), a phytotherapist was named. Three (3.1%) of the diet plans did not present any health professional in charge. However, one of these (33.3%) was based on the method for losing weight proposed by the French nutrologist Pierre Dukan and one (33.3%) was based on the method of the American physician Ian Smith.

DISCUSSION

In view of the large number of women's magazines that publish diet plans for weight loss, the results from this study raise concerns about the potential impacts on health from following these plans. Less than 20% of the 95 plans proposed diets with adequate carbohydrate content, less than 5% presented adequate saturated fatty acid content and less than 3% proposed diets with appropriate protein intake, according to WHO standards.[23,24]

Table 2. Quantitative analysis on the adequacy of provision for fiber and sodium.

Publication	Below recommendation		In line with recommendation		Above recommendation		Total	
	n	%	n	%	n	%	n	%
Fiber (g)								
Magazine A	10	90.9	1	9.0	0	0.0	11	
Magazine B	15	71.4	6	28.5	0	0.0	21	
Magazine C	14	82.3	3	17.6	0	0.0	17	
Magazine D	20	80.0	5	20.0	0	0.0	25	**100.0**
Magazine E	15	100.0	0	0.0	0	0.0	15	
Magazine F	5	83.3	1	16.6	0	0.0	6	
Total	**79**	**83.1**	**16**	**16.8**	**0**	**0.0**	**95**	
Sodium (mg)								
Magazine A	2	18.1	8	72.7	1	9.0	11	
Magazine B	9	42.8	7	33.3	5	9.0	21	
Magazine C	6	35.2	10	58.8	1	5.8	17	
Magazine D	6	24.0	14	56.0	5	20.0	25	**100.0**
Magazine E	6	40.0	7	46.6	2	13.1	15	
Magazine F	2	33.3	3	50.0	1	16.6	6	
Total	**31**	**32.6**	**49**	**51.5**	**15**	**15.7**	**95**	

Table 3. Quantitative analysis on the adequacy of provision for vitamin C and iron.

Publication	Below recommendation		Risk of inadequacy		In line with recommendation		Above recommendation		Total	
	n	%	n	%	n	%	n	%	n	%
Vitamin C (mg)										
Magazine A	2	18.1	0	0.0	9	81.8	0	0.0	11	
Magazine B	0	0.0	1	4.7	19	90.4	1	4.7	21	
Magazine C	1	5.8	0	0.0	16	94.1	0	0.0	17	
Magazine D	2	8.0	1	4.0	22	88.0	0	0.0	25	**100.0**
Magazine E	1	6.6	0	0.0	14	93.3	0	0.0	15	
Magazine F	0	0.0	1	16.6	5	83.3	0	0.0	6	
Total	**6**	**6.3**	**3**	**3.1**	**85**	**89.4**	**1**	**1.0**	**95**	
Iron (mg)										
Magazine A	2	18.1	9	81.8	0	0.0	0	0.0	11	
Magazine B	6	28.5	15	71.4	0	0.0	0	0.0	21	
Magazine C	5	29.4	12	70.5	0	0.0	0	0.0	17	
Magazine D	9	36.0	16	64.0	0	0.0	0	0.0	25	**100.0**
Magazine E	4	26.6	11	73.3	0	0.0	0	0.0	15	
Magazine F	1	16.6	4	66.6	1	16.6	0	0.0	6	
Total	**27**	**28.4**	**67**	**70.5**	**1**	**1.0**	**0**	**0.0**	**95**	

Simple exclusion of food sources of carbohydrates such as fruits, vegetables and grains from an individual's usual diet will typically lead to a calorie deficit of approximately 500 calories per day, thus resulting in a loss of 0.45 to 0.9 kg per week. In turn, diet plans that reduce or restrict carbohydrate consumption lead to a loss of 2 to 3 kg in the first week.[10] This extra loss is not due to a change in metabolism, which would lead to an increase in lipolysis, but to increased diuresis induced by the diet. Even by increasing the 24-hour energy expenditure from 2% to 3%, this effect is responsible for only a small fraction of the weight loss.[10,33] Because low carbohydrate diet plans restrict consumption of fruit and vegetables, they are notoriously deficient in micronutrients.[33]

A systematic review compared the effects of low carbohydrate/high protein (LC/HP) versus low fat/high carbohydrate (LF/HC) diet plans on weight loss. At six months, there were weight reduction of up to 4.02 kg in favor of the LC/HP plan ($P < 0.00001$); but after 12 months, this difference dropped to 1.05 kg ($P < 0.05$). Evidence from this systematic review shows that LC/HP diets are more effective than LF/HC diets for weight reduction at 6 months, but their effectiveness decreases by the 12th month.[34]

A prospective Japanese study involving two cohorts that were followed for 9 to 14 years tested the hypothesis that the intake of saturated fatty acids is inversely associated with the risk of stroke and directly associated with coronary heart disease. The investigators reported that there was a direct association between saturated fatty acid intake and myocardial infarction, mainly among men. On the other hand, they found an inverse association between saturated fatty acid intake and ischemia.[35]

Only 16.8% of the 95 diet plans provided fiber content within the DRI recommendations.[25] Fibers have important physiological effects, including prevention of intestinal diseases, treatment of obesity and reduction of serum lipid levels.[11,36-39] From a meta-analysis on 67 randomized trials assessing the effect of dietary fiber on serum cholesterol levels, it was found that the consumption of 2-10 g of soluble fibers per day was associated with a significant reduction in total cholesterol levels.[38]

Almost 70% of the diet plans did not specify the total daily quantity of calories, and in over half of those that provided this information, it was incorrect. All diet plans that propose reductions in total daily calorie intake will lead to weight loss. In the absence of physical activity, a plan that provides between 1400 to 1500 calories per day, regardless of the macronutrient percentage, will result in weight loss.[40]

A previous Brazilian study published in 2004 also assessed diet plans for weight loss that were featured in non-scientific publications. The authors reported that 80% of the diet plans did not provide any information on daily intake of water and less than 25% had appropriate macronutrient distributions. In fact, all of the plans had inadequate protein content, with one third of them recommending that over 15% of the total calorie intake should come from that macronutrient. Moreover, 86% of those plans provided inappropriate calcium content, 92% gave rise to inadequate vitamin E content and 97% did not provide adequate iron content.[12] In our study, carried out ten years later, 20% of the diet plans did not provide any information on daily intake of water and less than 4% had appropriate macronutrient distributions. In relation to protein, 97.8% of them recommended that over 15% of the total calorie intake should come from that macronutrient. The vitamin E content of the diet plans was not verified in this study, but 75.7% of the plans presented a probability of being inadequate in relation to calcium and 70.5% did not provide adequate iron content.

Less than 13% of the diet plans provided adequate calcium content. Calcium is an essential mineral at different stages of women's lives, especially with regard to maintaining bone health.[26,41] Consumption of high protein diets, especially for long periods, may cause increased urinary calcium loss, thus increasing the risks of osteoporosis.[42,43] A prospective Norwegian study reported that there was a significantly higher risk of hip fracture among women with high intake of non-dairy animal protein and low calcium intake (RR 1.96; 95% CI 1.09-3.56).[44]

The lack of recommendations about water intake in most diet plans for weight loss that are available in popular women's magazines is worrying. Under normal environmental conditions and energy expenditure, an average adult will need approximately 1 ml of water per calorie. The need will be higher among individuals who have an exercise routine and among those who are on a protein-rich diet. Deficiency in water intake manifests quickly and a change in the body's water content as small as 1% promptly causes symptoms of dehydration.[45]

Almost two thirds of the plans included in our study did not encourage physical activity along with the diet, despite the well-known fact that exercise is an important part of any weight loss and maintenance program.[44,46,47]

Although our study did not evaluate the readers' actual use of the diets or the possible impact of the dietary plans on their health, it clearly shows that most diets published in popular Brazilian women's magazines are inadequate. Our results are important for informing the general public about the risks of blindly following the diets published in these magazines and to alert journalists and editors of these publications about the need to check the scientific accuracy and safety of these diet plans before disseminating them to a wide lay audience.

CONCLUSION

All of the 95 diet plans for weight loss published during a six-month period in popular Brazilian women's magazines failed to follow one or more of the international dietary recommendations. In this light, the results obtained here emphasize that

publication of diet plans for weight loss in non-scientific magazines needs to be based on international dietary recommendations and evidence from studies of good methodological quality. Following these diets may cause deleterious effects to health.

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Are there differences in birth weight according to sex and associations with maternal exposure to air pollutants? A cohort study

Existem diferenças no peso ao nascer de acordo com sexo e associações com exposição materna a poluentes do ar? Estudo de coorte

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KEY WORDS:
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PALAVRAS-CHAVE:
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Ozônio.
Recém-nascido de baixo peso.
Material particulado.
Poluição do ar.

ABSTRACT

CONTEXT AND OBJECTIVE: Several effects of exposure to air pollutants on human health are known. The aim of this study was to identify whether exposure of pregnant women to air pollutants contributes towards low birth weight and which sex is more affected.

DESIGN AND SETTING: Longitudinal study using data on newborns from mothers living in São José do Rio Preto (SP) who were exposed to air pollutants in 2012-2013.

METHODS: A hierarchical model on three levels was built using maternal and newborn variables and environmental concentrations of particulate matter, ozone and nitrogen dioxide in quartiles. Preterm newborns, twins and newborns with birth defects were excluded and exposure windows of 30, 60 and 90 days before delivery were considered.

RESULTS: 8,948 newborns were included: 4,491 males (50.2%) and 4,457 females (49.8%); 301 newborns presented low birth weight (3.4%). The mean weight differed between males (3281.0 g) and females (3146.4 g) ($P < 0.001$). Exposure to ozone was significantly associated with low birth weight in both sexes in the 30-day window (odds ratio, OR = 1.38) and 90-day window (OR = 1.48); and among females, in the 30-day window (OR = 1.58) and 90-day window (OR = 1.59). Exposure to particulate matter had a paradoxical protective effect. No association was found among male newborns.

CONCLUSIONS: Female newborns showed greater susceptibility to maternal exposure to air pollutants. Studies on low birth weight in relation to maternal exposure to air pollutants should deal with males and females separately.

RESUMO

CONTEXTO E OBJETIVO: São vários os efeitos da exposição a poluentes do ar na saúde humana. O objetivo deste estudo foi identificar se a exposição da gestante contribui para o baixo peso ao nascer e qual o sexo mais acometido.

TIPO DE ESTUDO: Estudo longitudinal com dados de recém-nascidos de mães residentes em São José do Rio Preto (SP) com exposição a poluentes do ar em 2012 e 2013.

MÉTODOS: Foi construído modelo hierarquizado em três níveis com variáveis maternas, do recém-nascido e concentrações de material particulado, ozônio e dióxido de nitrogênio, em quartis. Foram excluídos recém-nascidos prematuros, gemelares ou com malformações e consideradas janelas de exposição de 30, 60 e 90 dias anteriores ao parto.

RESULTADOS: Foram incluídos 8.948 recém-nascidos, 4.491 do sexo masculino (50,2%) e 4.457 do feminino (49,8%), e identificados 301 recém-nascidos com baixo peso (3,4%). Os pesos médios foram diferentes entre o sexo masculino (3.281,0 g) e o feminino (3.146,4 g) ($P < 0,001$). Exposição ao ozônio esteve associada significativamente ao baixo peso ao nascer em ambos os sexos nas janelas de 30 dias (*odds ratio*, OR = 1,38) e 90 dias (OR = 1,48) e, no sexo feminino, nas janelas de 30 dias (OR = 1,58) e 90 dias (OR =1,59). Exposição ao material particulado teve efeito protetor paradoxal. Não houve associação no sexo masculino.

CONCLUSÕES: Houve maior susceptibilidade do sexo feminino aos poluentes a partir da exposição materna. Estudos sobre baixo peso ao nascer segundo exposição materna a poluentes do ar devem separar sexo masculino e feminino.

INTRODUCTION

Low birth weight (LBW), defined as birth weight less than 2,500 g and as small for gestational age, is a manifestation of intrauterine growth restriction, and it is a predictor of morbidity and mortality in the first year of life. LBW may be caused by changes to placental blood flow, weight gain deficit during pregnancy and active and passive smoking involving pregnant women.[1] In addition to these factors, the mother's exposure to air pollutants has also been identified as associated with LBW. The pollutants that have been associated with this outcome include particulate matter,[2-4] sulfur dioxide,[5-7] carbon monoxide,[3,4,8] nitrogen dioxide[3] and ozone.[4,6]

Fetuses, in particular, are considered highly susceptible to a variety of pollutants because of their physiological immaturity. Moreover, patterns of exposure occurring in certain windows that are sensitive periods for development because of higher rates of both cell proliferations and metabolic changes may increase fetal susceptibility.[9]

Regarding these windows, it seems that the effect of exposure to air pollutants may be greatest during the last trimester of pregnancy. This effect would be similar to that of active or passive maternal smoking, i.e. it would influence birth weight. The explanation for this is that fetal weight gain is very sharp from the 28th week of pregnancy onwards and involves release of hormones such as corticotrophin-releasing hormone (CRH) and placental adrenocorticotropic hormone (ACTH).[10,11]

Gender differences have been identified, such as higher birth weight among males, greater lung maturity among females and increased risk of neonatal and child mortality and increased risk of preterm birth among males.[12] Similarly, studies have been developed in an attempt to identify differences in the responses of males and females regarding the association between maternal exposure to air pollutants and low birth weight. Some studies has shown that males are more affected, while others have shown that females are more affected and yet others have not shown any association with the sex of the newborn.[12-15]

OBJECTIVE

The objective of this study was to identify possible differences in birth weight, according to sex, associated with maternal exposure to air pollutants in São José do Rio Preto (SP).

METHODS

This was a longitudinal study on live birth data carried out in São José do Rio Preto, covering the period from January 1, 2012, to December 31, 2013. The data were obtained from the Brazilian Live Births Information System (Sistema de Informações sobre Nascidos Vivos, SINASC).[16] Newborns from pregnancies that lasted for 37 weeks or more were selected for this data set. Twin deliveries and those with any type of congenital anomalies were excluded.

São José do Rio Preto is located in the state of São Paulo at 20° 49' S and 49° 22' W, at a distance of about 440 km from the state capital and the average annual temperature is 23.6°. The population comprises around 430,000 inhabitants in a 430-km^2 area. The municipality had an automobile fleet of just over 320,000 vehicles in 2012, and an urbanization rate of around 94.1%. It has 157 healthcare facilities. Its Human Development Index (HDI) is 0.79 and it is an important production center for sugar and alcohol.[17]

The mother and child variables included in this study were as follows: the mother's age (in years) was categorized as up to 19 years of age and above 34 years (at risk) or 20-34 years (non-risk); the number of children alive was categorized as none (non-risk) or one or more (at risk); the mother's marital status was categorized as living with partner or husband (non-risk) or living alone (at risk); the mother's education level was categorized as elementary education, i.e. up to 8 years of schooling (at risk), or beyond elementary level, i.e. 9 years of schooling or more (non-risk); the prenatal number of consultations was categorized as 0 to 6 (at risk) or 7 or more (non-risk); the newborn's sex (male or female); the newborn's weight (in grams) was categorized as LBW or normal weight (i.e. weighing greater than or equal to 2,500 g); and the type of delivery (vaginal or cesarean section).

The environmental variables comprised the average concentrations of particulate matter less than 10 μ of aerodynamic diameter (PM10); and nitrogen dioxide (NO_2) and ozone (O_3), quantified in $\mu g/m^3$. These were measured by the São Paulo state environmental agency (CETESB), at its location in the municipality. These concentrations were then transformed into mean exposures over 30, 60 and 90-day windows prior to the newborns' delivery.

Hierarchical unconditional logistic regression at three levels (distal, intermediate and proximal) was built to quantify the effect of pregnant women's exposure to air pollutants on the weight of their newborns, represented by the chance of having a newborn with low weight according to certain conditions.

The variables at the distal level (maternal age, parity, marital status and educational level) were analyzed in univariate analysis together with the birth weight, which was categorized as normal or LBW. If $P < 0.10$, the variables were kept for multivariable analysis and were then maintained at this level if $P < 0.05$.

Following this, we analyzed the variable at the intermediate level (prenatal number of consultations). The next step was to analyze this variable using the variables from the previous level that presented $P < 0.05$. The variable of prenatal number of consultations would be adjusted in accordance with the variables of the previous level. The hierarchical model was built with two levels, comprising the distal and intermediate variables.

Next, we analyzed the proximal variables, which consisted of the pollutant concentrations categorized as non-risk. If the concentration was in first quartile, it was considered to be a reference, while the other quartiles made up the at-risk group. The distal variables with $P < 0.05$ were kept at this level, as described above.

The analyses were performed considering both sexes and then only with males and, separately, only with females. These analyses were performed with pollutants categorized into quartiles and adjusted in accordance with the distal and intermediate level variables.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17. The significance level used was alpha = 5%.

This study was conducted using data available in a public access database without the possibility of identifying the subject. Thus, it was not submitted to a research ethics committee for approval.

RESULTS

The study included 8,948 infants, consisting of 4,491 males (50.2%) and 4,457 females (49.8%), born between January 1st, 2012, and December 31st, 2013. The mean birth weight was 3213.9 g (standard deviation, SD = 416.4), with a range from 870 g to 5420 g. There were 301 newborns with low birth weight (3.4%), according to the exclusion criteria, such as pregnancy to term, single pregnancy and no malformation. The average weights according to the newborn's sex were 3281.0 g (standard deviation, SD = 419.6) for males and 3146.4 g (SD = 402.0) for females ($P < 0.001$).

The odds ratio (ORs) and respective 95% confidence intervals (95% CIs) of the independent variables according to low birth weight and normal weight among the newborns are shown in **Table 1**. It was found that there was a significantly higher chance of low birth weight among female newborns (OR = 1.39) and among the newborns of mothers without a partner (OR = 1.28), mothers who made fewer prenatal care visits (OR = 2.45), mothers whose educational level was lower (OR = 1.59) and mothers who were under the age of 20 years and over the age of 34 years (OR = 1.29).

The distribution of mean pollutant levels according to 30, 60 and 90-day windows before the newborns' delivery is shown in **Table 2**. The maximum values for these concentrations did not exceed the values that are considered acceptable according to state of São Paulo Decree-Law no. 59,113, of April 23, 2013.[18]

Maternal education level, maternal age and marital status were variables from the distal level with $P \leq 0.10$. Maternal education level remained with $P < 0.05$ in the multivariate analysis, but marital status showed $P = 0.07$. However, because this was close to the significance level, this variable was retained due to its importance.

Inclusion of the intermediate-level variable (number of consultations), to be adjusted in accordance with the variables of the previous level, did not change its statistical significance. Thus, the hierarchical model contained two levels, comprising the variables of marital status, maternal education level and number of consultations.

Following this, the variables of the proximal level were introduced, i.e. pollutant concentrations in the 30, 60 and 90-day windows prior to the newborns' delivery, in two classes: at-risk and non-risk. The pollutants were included in the analysis one by one according to the 30, 60 and 90-day windows. Multi-pollutant analyses were carried out on the pollutants that showed $P < 0.10$ in the previous step and these variables were retained if $P < 0.05$, after adjustment for the possible variables of the same proximal level and those of the distal and intermediate levels.

The ORs according to exposure to pollutants, for both sexes, are shown in **Table 3**. Exposure to ozone was associated with low birth weight in the 30 and 90-day windows before the newborns' delivery and exposure to particulate matter was shown, paradoxically, to be protective against exposure to low birth weight in the 90-day window prior to the newborns' delivery. Ozone exposure was associated with the 30-day window (OR = 1.39; 95% CI: 1.05 to 1.85) and with the 90-day window (OR = 1.49; 95% CI; 1.10 to 2.00); exposure to PM10 showed a protective effect in the 90-day window (OR = 0.69; 95% CI: 0.54 to 0.88). No association was found for the 60-day window, or in relation to NO_2 exposure. In this step, the analysis was not adjusted for the variables of the previous levels.

Next, the ozone and particulate matter concentrations were adjusted for maternal educational level, marital status and number of consultations, for both sexes and separately for males

Table 1. Odds ratios (OR) with 95% confidence intervals (95% CI) and P-values of the maternal variables of age, education, marital status, number of prenatal consultations and delivery type and the newborns' sex, according to birth weight (low or normal). São José do Rio Preto, Brazil, 2012-2013

	Low	Normal	OR (95% CI)	P-value
Age				
20-34 years	208	6,421	1.00	0.045
≤ 19 and > 34 years	93	2,226	1.29 (1.01-1.66)	
Marital status				
Married	125	4,147	1.00	0.04
Single	173	4,470	1.28 (1.02-1.62)	
Schooling				
≤ 8 years	253	7,728	1.59 (1.15-2.18)	< 0.01
> 8 years	47	905	1.00	
Prenatal consultations				
0-6	221	7,528	2.45 (1.88-3.19)	< 0.01
≥ 7	79	1,098	1.00	
Gender				
Male	127	4,364	1.00	< 0.01
Female	174	4,283	1.39 (1.11-1.76)	
Delivery type				
Vaginal	56	1,195	1.00	0.02
Cesarean	245	7,452	1.42 (1.06-1.92)	

and for females. It could be seen that there was no significant association for males in any exposure window. For both sexes, there were significant associations between exposure to ozone and LBW in the 30-day window and 90-day window. Significant exposures for females occurred in the 30-day window and the 90-day window. Maternal exposure to PM10 had a paradoxical protective effect when the analysis did not consider gender distinction (**Table 4**).

In the 30-day windows, without distinction between the sexes, maternal exposure to ozone increased the risk of low birth weight from 6.6% to 8.8%; regarding females, the risk increased from 8.2% to 12.3%.

Table 5 shows the odds ratios obtained from multipollutant analysis on maternal exposure and LBW. For both sexes and for female newborns, exposure to PM10 had a paradoxical protective effect; on the other hand, maternal exposure to ozone had a significant correlation for female newborns in 90 days window and for both sexes. In this window, maternal exposure to ozone increased the risk of low birth weight from 7.7% to 11.0% without distinction between the sexes; for females, the risk increased from 10.0% to 15.1%.

DISCUSSION

This was, to the best of our knowledge, the first Brazilian study on the effect of maternal exposure to air pollution during pregnancy and low birth weight, categorized according to the newborns' sex. Maternal exposure to ozone in the 30 and 90-day windows prior to birth was seen to be associated with low birth weight, and this association was only with female newborns.

The prevalence of low birth weight in this study was 3.4%, which was lower than the prevalences found for Brazil (8.3%) and the state of São Paulo (9.2%) over this period. However, it is

Table 2. Mean concentrations of the pollutants NO_2, PM10 and ozone (in μg/m³) with standard deviations (SD), minimum values (Min), maximum values (Max) and percentiles 25 (P25), 50 (P50) and 75 (P75), during the 30, 60 and 90-day windows prior to the newborns' delivery. São José do Rio Preto, Brazil, 2012-2013

	Mean (SD)	Min-Max	P25	P50	P75
30-day window					
NO_2	48.04 (9.36)	30.87-70.13	40.88	46.16	55.16
PM10	44.31 (14.37)	21.68-85.45	33.82	42.90	54.13
Ozone	54.81 (6.13)	37.87-70.97	52.97	53.99	58.48
60-day window					
NO_2	48.92 (10.10)	33.84-65.96	40.19	47.32	52.87
PM10	44.68 (13.80)	19.81-75.00	34.94	45.62	54.52
Ozone	56.05 (5.72)	42.84-79.79	52.87	52.22	58.18
90-day window					
NO_2	49.22 (10.62)	31.57-69.04	39.97	48.18	58.78
PM10	44.30 (13.69)	17.78-65.66	33.47	47.19	53.74
Ozone	57.86 (7.25)	46.53-81.98	52.36	56.72	60.48

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for presence (1) and absence (0) of low birth weight (LBW), according to concentrations of the pollutants ozone, particulate matter (PM10) and nitrogen dioxide (NO_2), during the 30, 60 and 90-day windows prior to the newborns' delivery, without adjustment and without distinction between the sexes. São José do Rio Preto Brazil - 2012-2013

	LBW	30 days	60 days	90 days
Ozone	0	1.00	1.00	1.00
	1	**1.39(1.05-1.85)***	1.19 (0.91-1.55)†	**1.49 (1.10-2.00)***
PM10	0	1.00	1.00	1.00
	1	0.84 (0.65-1.08)†	0.87 (0.67-1.13)†	**0.69 (0.54-0.88)***
NO_2	0	1.00	1.00	1.00
	1	1.06 (0.81-1.38)†	0.94 (0.72-1.22)†	0.85 (0.66-1.10)†

*P < 0.05; †P > 0.10.

Table 4. Odds ratios (OR) with 95% confidence intervals (95% CI) for presence (1) and absence (0) of low birth weight (LBW), according to ozone and PM10 exposure, singly, adjusted for marital status, maternal schooling and number of consultations during the 30 and 90-day windows, for both sexes and separately for males and females. São José do Rio Preto (SP), Brazil, 2012-2013

	LBW	Both sexes*	Males	Females
Ozone, 30 days	0	1.00	1.00	1.00
	1	**1.38 (1.03-1.84)†**	1.17 (0.76-1.79)	**1.58 (1.06-2.34)†**
Ozone, 90 days	0	1.00	1.00	1.00
	1	**1.48 1.10-2.00)‡**	1.35 (0.86-2.11)	**1.59 (1.06-2.40)‡**
PM10, 90 days	0	1.00	1.00	1.00
	1	**0.72 (0.56-0.92)‡**	0.70 (0.48-1.02)	0.72 (0.52-1.00)

*Without distinction between the sexes; †P = 0.03; ‡P = 0.02.

Table 5. Odds ratios (OR) with 95% confidence intervals (95% CI) for presence (1) and absence (0) of low birth weight (LBW), according to particulate matter (PM10) and ozone exposure, adjusted for marital status, maternal schooling and number of consultations during the 90-day windows, for both sexes and separately for males and females. São José do Rio Preto (SP), Brazil, 2012-2013

	LBW	Both sexes*	Males	Females
Ozone,	0	1.00	1.00	1.00
90 days	1	**1.50 (1.11-2.02)**‡	1.36 (0.86-2.13)	**1.61 (1.07-2.42)**†
PM10,	0	1.00	1.00	1.00
90 days	1	**0.72 (0.56-0.91)**†	0.70 (0.48-1.01)	**0.72 (0.51-0.99)**†

*Without distinction between the sexes; †P = 0.03; ‡P = 0.02.

necessary to consider the exclusion factors that must have contributed to these results.[16]

The newborns with low birth weight in this study were significantly associated with lower and higher maternal ages[20] (≤ 19 years and > 34 years), mothers living without a partner (single or separated), lower education level, fewer than seven prenatal visits and female sex. These findings coincide with those found by Haidar et al.[19]

The daily means for PM10, NO_2 and ozone exposures in the 30, 60 and 90-day windows before the newborns' delivery did not exceed the limits deemed to be acceptable through a state decree that established new air quality standards for the state of São Paulo, based on the guidelines established by WHO.[18] These values for ozone were lower than those found in São José dos Campos (67.8 μg/m³),[6] but higher than those found in Rio de Janeiro (44.5 μg/m³).[20] For PM10, the values in São José do Rio Preto were higher than in São José dos Campos (35.2 μg/m³),[6] and lower than in Rio de Janeiro (59 μg/m³).[20]

Bobak[7] found an association with exposure to SO_2 when this occurred in the third trimester of pregnancy, with OR = 1.27 for an increase of 50 μg/m³ when concentrations were of the order of 32 μg/m³ at the study site. Likewise, exposure to total suspended particles (TSP), which are particles of liquid or solid material suspended in the air in the shape of dust, mist or aerosol of less than 50 microns in diameter (which includes PM10), was significant during the first trimester of pregnancy, with OR = 1.18 for an increase of 50 μg/m³ in the concentration of this pollutant, for which the mean value was 72 μg/m³. These pollutants had not been quantified in São José do Rio Preto. PM10 showed paradoxical protective behavior in relation to exposure over the 90-day window before the newborns' delivery, for both sexes and for males, with OR = 0.50 (95% CI: 0.29 to 0.86) and OR = 0.40 (95% CI: 0.16 to 0.98), respectively.

Medeiros and Gouveia[3] identified an association between exposure to CO, PM10 and NO_2 in the first trimester of pregnancy and LBW. In our study, it was not possible to find this association, possibly because the PM10 and NO_2 concentrations were lower than those found in São Paulo, at the time of our study. In Rio de Janeiro too, no associations were identified between exposure to PM10, CO and NO_2 and LBW, even with PM10 and NO_2 concentrations higher than those found in São José do Rio Preto.[20]

In São José dos Campos (SP), a city in southeastern Brazil, maternal exposure to SO_2 and ozone, over the 90 days before the newborns' delivery was associated with LBW. The average concentrations were of the order of 6 μg/m³ for SO_2 and 66 μg/m³ for ozone, and these mean concentrations of ozone were similar to those found in São José do Rio Preto.[6] In a review, Maisonet et al. cited that exposure to SO_2 was associated with LBW, but this pollutant is not monitored in São José do Rio Preto. On the other hand, NO_2 levels were not significantly associated with LBW either in the study by Maisonet et al. or in São José do Rio Preto.[21] In another review, Sram et al.[9] reported that exposure to SO_2 was significant, including exposure in the last trimester of pregnancy and that exposure to NO_2 was only sometimes associated with LBW. Exposure to ozone was not associated with LBW or with intrauterine growth restriction in that review.

Liu et al. also did not find that exposure to ozone and NO_2 was associated with LBW, either in the first or in the last month of pregnancy, after adjustment for maternal age, parity, newborn sex, gestational age and birth season, in a study carried out in Vancouver, Canada.[22] The mean concentrations of these pollutants were of the order of 60 and 70 μg/m³ for ozone and NO_2 respectively, and these values were not very different from those found in São José do Rio Preto.

On the other hand, a study carried out in southern California, a region with great variability of concentrations of air pollutants, showed that exposure to ozone had a significant deleterious role in relation to birth weight when this exposure occurred during the last trimester of pregnancy. Analysis on the pollutants individually showed a reduction of 37 g in birthweight secondary to the exposure to 70 μg/m³. When associated with PM10, an increase in ozone concentration of the order of 35 μg/m³ implied a significant reduction of 32 g in the newborns' weight. This increase of 35 μg/m³ was associated with a decrease of 37 g in birth weight when the pollutants CO and NO_2 were included in the model. Exposure to PM10 and NO_2 in the third trimester was not associated with decreased weight among the infants.[4]

In a study conducted in Nova Scotia, Canada, where the average concentrations of ozone and PM10 were 45 μg/m³ and 17 μg/m³ respectively, it was not possible to identify any significant association between exposure to these pollutants in the third trimester of pregnancy and low birth weight. Exposure to PM10 in the first trimester of pregnancy was associated with low birth weight. The authors proposed a hypothesis of abnormal

placental development and increased blood viscosity, due to an inflammatory response or the action of polycyclic aromatic hydrocarbons.[23] Compared with our findings, the average concentrations found in Canada were lower than those found in São José do Rio Preto.

In the present study, without adjustment for other variables and without stratifying according to sex, ozone exposure was significant when it occurred in the 30 and 90-day windows before the newborns' delivery. The chance of LBW was more evident with concentrations greater than 53 μg/m^3. Exposure to ozone was shown to be a significant risk factor in the study by Salam et al.,[4] with OR = 1.41, and in São José dos Campos (OR = 1.26).[6] However, there was no association in other studies.[8,19] In São José do Rio Preto, an association with ozone exposure was identified only among females.

We also observed that maternal exposure to PM10 showed paradoxical behavior over the 90-day period before birth, in that this exposure was reflected as a protective factor, with OR = 0.72 for both sexes and also for females. These values diverge from those found in other studies,[3,4,6] even with similar concentrations. Our study considered homogeneous concentrations quantified at fixed monitoring stations. However, the distance from homes to roads with heavy traffic, distance-weighted traffic density (DWTD) and land use regression levels of particulate matter (LUR-PM10) were not considered as in the study by Habermann and Gouveia.[24] These authors found that LBW was associated with DWTD and LUR-PM10 in the highest quartiles of exposure, with a significant linear trend of decrease in risk. We found that high maternal socioeconomic status, as assessed through higher educational level, had a protective effect against low birth weight. On the other hand, living in areas of higher vehicular traffic might not in fact give rise to greater expose to air pollution and the protection against LBW arising from better socioeconomic status might also be stronger than the effect of exposure to air pollution. This exposure may not have been sufficient to increase the risk of LBW for these mothers. Regarding particulate matter constituents, Basu et al.[25] found that the largest reductions in birth weight were associated with exposure to vanadium, sulfur, sulfate, iron, elemental carbon, titanium, manganese, bromine, ammonium, zinc and copper, which were present as particulate matter constituents and were associated with increased risk of term LBW. In the stratified analysis according to sex, there were no differences.

No association between exposure to NO_2 and LBW was found in our study. Our findings are consistent with those of some other studies,[1-3] but are the opposite of those reported by Bell et al., who found that there was a decrease in weight of 9 g for each 10 μg/m^3 increase in NO_2 concentration.[15]

A significant association ($P < 0.05$) between exposure to ozone and LBW was identified in both the 30 and the 90-day windows before the newborns' delivery. This analysis on ozone was adjusted for the variables of the previous levels (maternal education, marital status and prenatal number of consultations), considering both sexes and females separately. With inclusion of PM10 concentrations, exposure to ozone during the 90-day window was significant, considering both sexes and females separately.

Exposure to PM10 showed paradoxical protective behavior for both sexes, over the 30-day and 90-day windows before the newborns' delivery. Salam et al. found that there was no significant association regarding exposure to PM10 during the last trimester of pregnancy. The mean concentrations found by these authors were similar to those in São José Rio Preto. The behavior of exposure to PM10 may have been an adjustment outcome for this pollutant when analyzed with ozone, or it may have been due to the composition and amount of material adsorbed on the particle, which depends on the study site.[4]

In the analysis according to the newborns' sex, there was no significant association between maternal exposure to ozone and PM10 and low birth weight among males in any of the windows (30, 60 and 90 days) before delivery. For PM10, there was paradoxical behavior regarding exposure over the 30 and 90-day windows before delivery. For females, an association between maternal exposure and LBW was evident over the 30 and 90-day windows. The effect was larger over the 90-day window, in the second quartile (OR = 2.97). An association between ozone exposure and LBW had already been observed in São José dos Campos, Brazil,[6] but not in other Brazilian studies. Regarding the effect among females, few studies have analyzed ozone and LBW and these either did not discriminate according to sex or the results were inconclusive.[15,26] In a study conducted in Poland, a larger LBW effect was found among male newborns, but the pollutant analyzed was PM2.5.[13] An association with exposure to ozone in the third trimester was identified by Ha et al. in Seoul (OR = 1.09; 95% CI: 1.04 to 1.14) when analyzed separately, but without any statistical significance in relation to other pollutants.[27]

The mechanisms that can lead to LBW because of ozone exposure are still unclear. In animals, particularly in pregnant rats, this effect can be modulated by inflammatory mediators, which make these animals more susceptible to acute lung inflammation because of impairment of the respiratory epithelial lining fluid. Since pregnant women have higher alveolar ventilation than non-pregnant women, the exposure level during pregnancy is likely to be higher, and similar inflammatory responses could be more pronounced in pregnant women. Moreover, inflammation due to ozone can result in release of products such as those associated with lipid peroxidation and circulating inflammatory cytokines. This may impair circulation and placental function and affect fetal growth.[4] In healthy human volunteers exposed to ozone, effects

were observed on biological markers, such as increased peripheral neutrophil levels and decreased ascorbic acid levels, upon exposure to 200 ppb (approximately 400 μg/m^3) of ozone for two hours. In an extensive review, Ghosh et al. stated that there was strong evidence that females were at higher risk of LBW with adjusted odds ratios ranging from 1.07 to 1.62. In addition, there was some evidence to suggest that the effects of air pollution on LBW may be differential according to sex. However, they did not cite any possible mechanisms.[12]

Our study may have some limitations, such as: the concentrations of pollutants were taken to be homogeneous throughout the city and it was assumed that pregnant women were exposed to these concentrations in a similar way; no information was obtained on diseases during pregnancy that might have affect the newborns' weight, such as smoking during this pregnancy, because the data source (SINASC), does not include this information; and, in addition, there was no information about the weight gain of the pregnant women. A further limitation may have arisen from the pregnant women's address information, because it is possible that the mother's residential address information and the length of time at this address (which would represent the length of time for which the mother was exposed to the pollutant concentrations studied) may not have corresponded to the reality. This study did not establish the cause between the exposure and outcome, but pointed towards possible associations.

Despite these limitations, the strength of this study is that, while pointing out the risks of exposure to air pollutants in the genesis of low birth weight, it identifies female newborns as more susceptible to impairment of birth weight, because of maternal exposure to ozone. This analysis suggests that in studies on the exposure of pregnant women to air pollutants, from which the outcome is low birth weight, it is necessary to separate the analysis between male and female newborns. Measures to reduce the concentration of pollutants in the air, particularly ozone, may reduce the prevalence of infants with low birth weight, thus reducing the risk of neonatal and infant mortality.

CONCLUSION

Female newborns showed greater susceptibility to maternal exposure to air pollutants. Studies on low birth weight in relation to maternal exposure to air pollutants should deal with males and females separately.

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Mammographic density among indigenous women in forested areas in the state of Amapá, Brazil: a cross-sectional study

Densidade mamográfica em mulheres indígenas de áreas da floresta do estado do Amapá, Brasil: estudo transversal

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KEY WORDS:
Polymorphism, genetic.
Receptors, estrogen.
Receptors, progesterone.
Health Services, indigenous.
Population groups.
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PALAVRAS-CHAVE:
Polimorfismo genético.
Receptores estrogênicos.
Receptores de progesterona.
Serviços de saúde do indígena.
Grupos populacionais.
Neoplasias da mama.

ABSTRACT

CONTEXT AND OBJECTIVE: There is no register of breast cancer cases among indigenous populations in Brazil. The objective here was to evaluate the association of clinical and demographic characteristics with mammographic density among indigenous women.

DESIGN AND SETTING: Cross-sectional analytical study conducted in indigenous territories in the state of Amapá, Brazil.

METHODS: Women were recruited from three indigenous territories and underwent bilateral mammography and blood collection for hormonal analysis. They were interviewed with the aid of an interpreter. Mammographic density was calculated using computer assistance, and was expressed as dense or non-dense.

RESULTS: A total of 137 indigenous women were included in this study, with an average age of 50.4 years, and an average age at the menarche of 12.8 years. Half (50.3%) of the 137 participants had not reached the menopause at the time of this study. The women had had an average of 8.7 children, and only two had never breastfed. The average body mass index of the population as a whole was 25.1 kg/m^2. The mammographic evaluation showed that 82% of women had non-dense breasts. The clinical characteristics associated with mammographic density were age ($P = 0.0001$), follicle-stimulating hormone (FSH) ($P < 0.001$) and estrogen levels ($P < 0.01$).

CONCLUSIONS: The majority of the indigenous women had non-dense breasts. Age, menopausal status and FSH and estrogen levels were associated with mammographic density.

RESUMO

CONTEXTO E OBJETIVO: Não há registro de casos de câncer de mama em populações indígenas no Brasil. O objetivo foi avaliar a associação de características clínicas e demográficas com a densidade mamográfica em mulheres indígenas.

TIPO DE ESTUDO E LOCAL: Estudo transversal, analítico, realizado em territórios indígenas no estado do Amapá, Brasil.

MÉTODOS: Mulheres foram recrutadas de três territórios indígenas e submetidas a mamografia bilateral e a coleta de sangue para análise hormonal. As participantes foram entrevistadas com a ajuda de um intérprete. A densidade mamográfica foi calculada com assistência de computador, e expressa como densa ou não densa.

RESULTADOS: 137 mulheres foram incluídas no estudo, com média de 50,4 anos e média de idade à menarca de 12,8 anos. Metade (50,3%) das 137 participantes não havia entrado na menopausa no momento do estudo. As mulheres tinham em média 8,7 filhos, e duas nunca haviam amamentado. O índice de massa corpórea médio da população como um todo foi de 25,1 kg/m^2. A análise mamográfica mostrou que 82% das mulheres tinham mamas não densas. As características clínicas associadas com a densidade mamográfica foram idade ($P = 0.0001$), hormônio folículo-estimulante (FSH, $P < 0,001$) e níveis de estrogênio ($P < 0,01$).

CONCLUSÃO: A maioria das indígenas tinha mamas não densas. Idade, *status* menopausal e níveis de estrógeno e FSH foram associados com a densidade mamográfica.

INTRODUCTION

It is known that breast cancer is less prevalent among African-American women than among white women. However, the disease onset is earlier among African-Americans, and these women have more aggressive tumors.[1,2] Women of indigenous origin clearly present lower incidences of breast cancer than women with no indigenous descent.[3-6]

The incidence of breast cancer in the indigenous population in Brazil is very low, and absolutely no cases have been found in some ethnic groups, such as the Xavantes group, living in the state of Mato Grosso.[7] This phenomenon can be explained by lifestyle habits: some peculiarities of indigenous populations are indeed protective factors, e.g. first pregnancy early in life, multiparity, prolonged breastfeeding and absence of hormone therapy. The hypotheses for explaining the lower incidence of breast cancer among indigenous women may include lower life expectancy and underreporting.[7] However, indigenous populations also present some risk factors for breast cancer: sedentary lifestyle, overweight and obesity are observed in more than half of these women.[3]

Breast density, as evaluated by mammography (mammographic density), is an independent risk factor for breast cancer, which is independent of age, menopausal status or exogenous steroid use.[8-12] To our knowledge, there is no other study in the literature addressing the relationship between demographic and clinical factors and mammographic density among indigenous women in Brazil.

OBJECTIVE

This study aimed to evaluate clinical and demographic characteristics and their association with mammographic density among indigenous women.

METHODS

Study design, participants and ethics

In this cross-sectional analytical study, indigenous women in Oiapoque, in the Brazilian state of Amapá, were evaluated. These women were recruited in three indigenous territories, Uaça, Galiby and Juminã, which are home to four indigenous ethnicities: Karipuna, Galibi Marworno, Palikúr and Galibi Kalina, distributed in 38 villages. The total population of these indigenous territories in 2010 was 7,021, according to figures from the local technical coordination office of the National Indian Foundation, in Oiapoque.

To evaluate these women, it was necessary to obtain authorizations from the indigenous leaders of Oiapoque, from the National Indian Foundation (FUNAI) and from the National Health Foundation (FUNASA). Permission from the indigenous leaders was obtained for this study after we participated in the annual meeting of the Association of Indigenous Peoples of Oiapoque (APIO), at which the research project was presented to the community. An informed consent form was signed by all the women to be examined, after the study objectives had been explained to them by a local interpreter, in the local Indian Community Center during the interview. Ethical approvals were obtained from the National Committee for Research Ethics (CONEP) and the local Ethics Committee of the university hospital.

The inclusion criteria were that the women needed to be 40 years of age or older, living in indigenous villages (and not in cities) and not using hormonal medications (including plant hormones) to treat menopausal symptoms during the 12 months preceding the interview. Women suffering from endocrine, liver or kidney disorders, as ascertained from the local medical records kept by FUNAI and FUNASA, were also excluded. Mammograms that were classified as Breast Imaging Reporting and Data System (BI-RADs) category 3 or above also constituted an exclusion criterion *a priori*.

From January to December 2009, it was possible to obtain authorizations and arrange transportation to examine 150 indigenous women. All of them, except for nine with age disparities and two with BI-RADs category 3, underwent blood collection for follicle-stimulating hormone (FSH) and estradiol tests and underwent mammography.

The subjects were transported by bus to the nearest big city to undergo mammography exams. Because they live in villages far from each other, the women were transported by boat or car from their villages to the Indian House, in the municipality of Oiapoque, and from this place they were transported by bus, for about 450 km, to another Indian House, in the city of Macapá, where they were interviewed by the principal investigator and a nurse technician. After the women had signed the informed consent form, blood samples were collected from them to assay for FSH and estradiol (E2). About 5 ml of peripheral blood were obtained from each subject, using a vacuum extraction tube containing the anticoagulant EDTA (ethylenediaminetetraacetic acid). For mammography, the women were then transported to Hospital São Camilo in Macapá.

All the women included in this study underwent analogue bilateral mammography on the same device (Lorad Affinity, with Kodak M35 X-OMAT processor and Kodak Min-R 2000 film). Two projections were obtained for each breast: mediolateral oblique (MLO) and craniocaudal (CC). The same radiologist who performed the examinations made the first classification of cases in accordance with the BI-RADS criteria, for confirmation of enrollment in the study. Women with mammographic scans in BI-RADS categories 1 and 2 of the American College of Radiology (ACR), i.e. indicating absence of changes suggestive of breast cancer, were included in this study. We then calculated mammographic density using the method described below.

Mammographic density evaluation

Firstly, two independent examiners evaluated the scans to determine the mammographic density. They worked subjectively, based on the mammographic patterns described in the ACR's BI-RADS 2003 manual.[1] The ratings D1, D2, D3 and D4 were grouped two-by-two to enable statistical analysis: D1 + D2 were considered to represent non-dense breasts and D3 + D4, dense breasts.

The mediolateral oblique incidence scans were then digitized (scanner CX312.T, Radiographic Digital Imaging, Compton, CA, USA). Following this, a third evaluator assessed mammographic density by using computer software for image analysis. Mammographic density was calculated using the gray-scale histogram tool of the Adobe Photoshop CS3 version 10.0 software as follows. The kappa coefficient was used to calculate the concordance between the three observers, two-by-two. Because the concordance was high ($r > 0.78$; $P < 0.001$), the third observer (called "computer-assisted evaluation" henceforth) was used as reference from then on.

Mammographic density was objectively determined using imaging analysis computer software. By convention, the mid-lateral left oblique incidence was scanned and captured using a CX312.T scanner (Radiographic Digital Imaging, Compton, CA, USA).

Initially, using the "Lasso Tool" (**Figure 1**), the image of the entire breast was selected, taking care to exclude the pectoral muscle. Through this procedure, the software generated a numerical value corresponding to the number of pixels in the overall breast area. Then, using the "Magic Tool", the densest area of the breast, corresponding to fibroglandular tissue, was selected to obtain the number of pixels of this area. Finally, the **Equation 1** was applied, to determine the percentage of fibroglandular tissue:

$$\text{Mammographic density (MD)} = \frac{\text{dense area (DA)} \times 100}{\text{total area}} \qquad (1)$$

The values obtained for the dense area were compared with the subjective values registered by the other two evaluators, and the concordance between them was calculated using the kappa coefficient.

Statistical analysis

The concordance between the three observers was calculated by means of the kappa coefficient, two-by-two. Because the concordance was high (kappa > 0.75), the evaluations of the third observer (henceforth referred to as "computer-assisted evaluation") were used as a reference. To decrease the number of classes within the computer-assisted evaluation variable, mammogram patterns were added as follows: D1 + D2 with the group of non-dense breasts; and D3 + D4 with the group of dense breasts.

The chi-square test was used for comparing qualitative variables (frequency and proportions). To compare quantitative data (mammographic density), the Mann-Whitney U test was used where necessary. When the expected frequency was less than 5, we used Fisher's exact test. To calculate odds ratios and confidence intervals, binary logistic regression was performed. Statistical significance was set at 5% or $P < 0.05$. The statistical software SPSS (Statistical Package for the Social Sciences), version 14.0, was used.

RESULTS

At the beginning of the study period, 150 women were recruited in the indigenous villages and were transported to undergo mammography. However, it was found that 9 of them were actually younger than 40 years, which prevented their inclusion in the study. Mammography was performed on the remaining 141 women, but 2 of them were classified as BI-RADS 3, which probably indicated benign lesions, for which follow-ups six months afterwards were suggested. Nevertheless, because this finding also constituted an exclusion criteria of the study, these 2 women were excluded. Thus, a total of 139 indigenous women whose mammograms

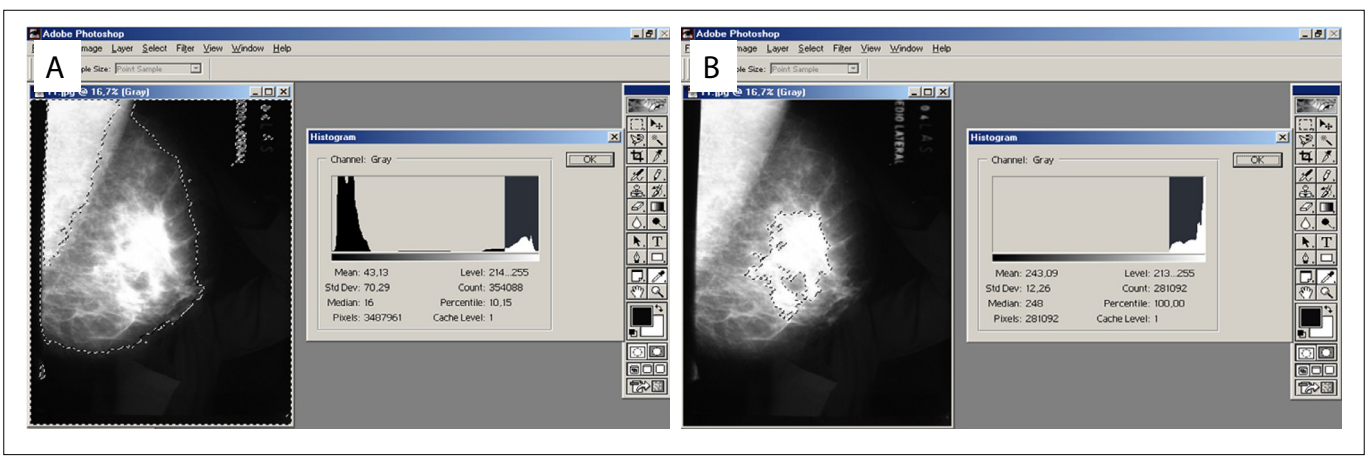

Figure 1. (A) Use of the "Lasso Tool" in Adobe Photoshop software, on a mammogram scan, for selection of the area to be calculated; and (B) "Magic Tool" for selection of dense tissue.

showed no signs of breast lesions were initially included in the study. However, in two cases, the mammogram film was damaged by moisture before it could be digitized for the analysis on mammographic density (**Figure 2**). The average age of the remaining 137 women initially included was 50.4 years, with the menarche at an average of 12.8 years (the earliest was at 10 years of age). About half (50.3%) of the women were premenopausal.

Only 10 of the women (0.7%) had a history of using hormonal contraceptives. Only one of them did not have any children. The total number of offspring of the 138 women who had children was 1,209, an average of 8.7 per mother; but more than half of them (57.2%) had 9 or more children, and one of them had 19.

The average age at which they had their first child was 15.4 years, and this ranged from 12 years of age (three women) to 22 years of age. All of the women except for five had had children before reaching 18 years of age. Half of them (50%) had had children before the age of 15.

Only two women (1.4%) had never breastfed: one without children and the other with six children. Ninety-eight women (70.5%) had breastfed for a minimum of 10 years. In relation to body mass index (BMI), 66 (47.4%) had a BMI indicating that they were overweight (≥ 25 kg/m^2). The average BMI of the population as a whole was 25.1 kg/m^2. None of the women interviewed had any history of alcoholism (defined as the equivalent of two doses of distilled spirits per day); 44 of them reported occasional alcohol use (31.6%), which was only at annual community festivals.

Most (68%) of the indigenous women were from two villages: Kumarumã (the Galibi Marworno people) and Espírito Santo (the Karipuna people). However, neither the subjects' tribe nor their village showed any significant association with any of the other variables of this study. Alcoholism (characterized as the equivalent of two servings of distilled liquor per day) was nonexistent in the sample (only occasional consumption of alcohol could be verified), which prevented calculation of any association with mammographic density. Nor did the distribution of origin (town or village) show any association with the main variables of the study. The Shapiro-Wilk test revealed that the sample data did not have normal distribution regarding the sociodemographic variables, so the Mann-Whitney test was used for the mammographic density association tests (as described below).

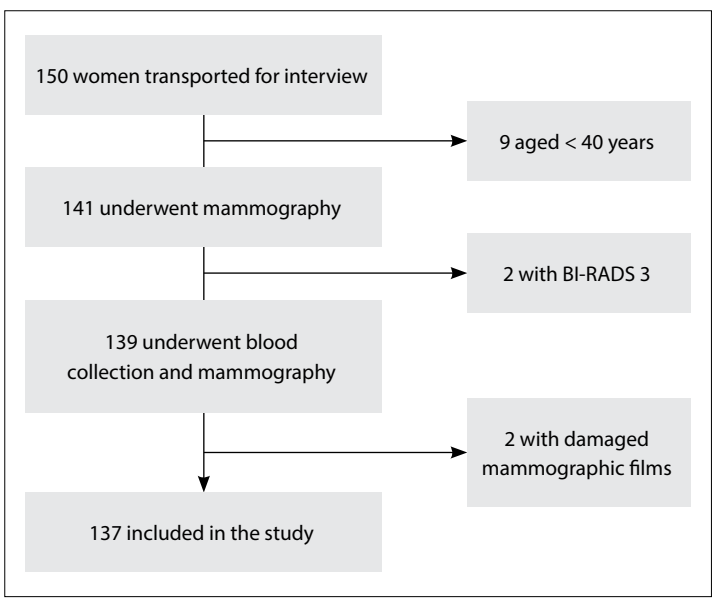

Figure 2. Flowchart of patients' recruitment and inclusion in the study.

Mammographic density

Among the 137 women for whom evaluation of mammographic density was possible, the distribution of the evaluations was classified as D1, D2, D3 and D4 (D = mammographic density). **Table 1** shows the number of evaluations made by each observer and the final average. As shown in **Table 2**, the three observations

Table 1. Distribution of mammographic density according to the observers

Mammographic density				
Classification	**Observer 1**	**Observer 2**	**Computer-assisted**	**Average**
D1	44 (32.1%)	43 (31.3%)	51 (37.2%)	46 (33.5%)
D2	63 (45.9%)	65 (47.44)	60 (43.7%)	63 (45.9%)
D3	28 (20.4%)	27 (19.7%)	24 (17.5%)	26 (18.9%)
D4	2 (1.45%)	2 (1.45%)	1 (0.72%)	2 (1.45%)
Total	**137**	**137**	**137**	**137**
Breast density patterns				
Density	**Observer 1**	**Observer 2**	**Computer-assisted**	
Non-dense	107 (78.1%)	108 (78.8%)	112 (81.7%)	
Dense	30 (21.8%)	29 (21.16%)	25 (18.2%)	
Total	**137**	**137**	**137**	

D1 to D4 refer to breast density classification; the least dense breast is D1 and most dense is D4.

Table 2. Agreement between observers, according to kappa coefficient, considering dense and non-dense mammographic densities together

	Coefficient	P-value
Computer-assisted versus observer 1		
Pearson's R	0.892	< 0.001
Spearman's correlation	0.892	< 0.001
Kappa	0.886	< 0.001
Computer-assisted versus observer 2		
Pearson's R	0.912	< 0.001
Spearman's correlation	0.912	< 0.001
Kappa	0.908	< 0.001
Observer 1 versus observer 2		
Pearson's R	0.979	< 0.001
Spearman's correlation	0.979	< 0.001
Kappa	0.978	< 0.001

(observers 1, 2 and the computer-assisted) were highly correlated (coefficient r > 0.8, with P < 0.001).

The D1, D2, D3 and D4 classifications were gathered into two groups to enable statistical analysis: thus, D1 + D2 were considered to be non-dense breasts and D3 + D4 to be dense breasts. Hence, as shown in **Table 1**, the majority of the cases were of non-dense breasts. The inter-observer concordance was also high when the classifications were grouped (D1 + D2) and (D3 + D4) (**Table 3**).

Mammographic density and association with other variables

Considering the high agreement (kappa) between the observers, we started to investigate associations with other variables, using the computer-assisted evaluation as a standard. Mammographic density was not significantly associated with any history of hormonal contraceptive use (P = 0.08) or with alcohol consumption (P = 1.00). Several other variables were also not associated with mammographic density (**Table 4**).

Two variables were significantly associated with mammographic density: serum levels of follicle-stimulating hormone (FSH) and estradiol (E2). Higher levels of FSH were associated with non-dense breasts (P = 0.001) and higher levels of E2, to dense breasts (P = 0.01). The participants' average age was significantly associated with mammographic density (**Table 4**).

There were 69 postmenopausal women and 68 were premenopausal. Most of the postmenopausal women had non-dense breasts (67; or 97%). Dense breasts were seen in two women after the menopause (3%) and 23 before (34%). The mammographic density was associated with the menopausal status (**Table 5**; P < 0.0001).

DISCUSSION

There is a high incidence of certain types of malignant tumors, such as colon, uterine and gastric cancers, in the Amazon region. However, absence of breast cancer among the indigenous women of several Brazilian states, such as Mato Grosso, Mato Grosso do Sul and Paraná, has been reported in the literature.[3,6,7] The National Health Foundation (FUNASA) keeps up-to-date records of the diseases that occur in the indigenous population, which undermines the hypothesis that underreporting is responsible for non-registration of cases of breast cancer among indigenous women in Brazil.[13] In the international literature, lower incidence of breast cancer has been reported in indigenous than in non-indigenous populations in the United States[14,15] and extremely low incidence was reported among indigenous women in Ecuador.[5] Breast cancer is more prevalent among women living in large cities.[2] Because dense breasts are an independent risk factor for breast cancer (and this risk persists for 10 years or more[16]), lower mammographic density might be a protective factor against breast cancer in indigenous populations.[17,18] That hypothesis inspired the present investigation, which was undertaken among women living in indigenous villages in the Amazon forest, far from urban areas. Because of this, these women were probably not subject to the lifestyle and dietary modifications seen in urban regions.

Table 3. Descriptive statistics on the frequency of hormonal contraceptive and alcohol use, and comparison with mammographic density using Fisher's exact test

Computer-assisted (3)		Hormonal contraceptive no	Hormonal contraceptive yes	Total	P
D1 + D2	N (%)	105 (94.6%)	6 (5.4%)	111 (100%)	
D3 + D4	N (%)	20 (83.3%)	4 (16.7%)	24 (100.0%)	0.08
Total	**N (%)**	**125 (92.6%)**	**10 (7.4%)**	**135 (100.0%)**	
Computer-assisted (3)		**Alcohol no**	**Alcohol yes**	**Total**	**P**
D1 + D2	N (%)	75 (67.6%)	36 (32.4%)	111 (100.0%)	
D3 + D4	N (%)	16 (66.7%)	8 (33.3%)	24 (100.0%)	1.00
Total	**N (%)**	**91 (67.4%)**	**44 (32.6%)**	**135 (100.0%)**	

Table 4. Clinical and hormonal characteristics of the indigenous women with non-dense (ND) and dense (D) breasts

		N	Mean	SD	P*
Age (years)	ND	112	51.95	10.19	< 0.001
	D	25	44.36	5.19	
BMI (kg/m^2)	ND	112	24.83	4.61	0.98
	D	25	26.21	9.98	
Age at menarche (years)	ND	112	12.9	1.07	0.52
	D	25	12.72	1.34	
Parity (N)	ND	112	8.82	3.15	0.27
	D	25	7.72	4.13	
FSH (mIU/ml)	ND	112	34.83	26.94	0.001
	D	25	14.77	21.14	
E2 (pg/ml)	ND	112	74.48	112.23	0.01
	D	25	83.12	83.06	
Age at first term pregnancy (years)	ND	110	15.38	1.38	0.43
	D	25	15.84	1.68	
Duration of breastfeeding (months)	ND	112	13.75	7.26	0.34
	D	25	11.86	7.28	

SD = standard deviation; BMI = body mass index; FSH = follicle-stimulating hormone; E2 = estradiol. *Mann-Whitney (z) test for non-parametrical variables.

Table 5. Distribution of dense and non-dense breasts according to menopausal status

Menopause	Dense	Non-dense	Total	P
Yes	2	67	**69**	
	3%	97%	**100%**	
No	23	45	**69**	
	34%	66%	**100%**	
Total	**25**	**112**	**137**	**< 0.0001**
	18%	**82%**	**100%**	

Several studies have shown lower mammographic density in women of indigenous ethnicity. This may have been due not only to their reproductive pattern of bearing many children, with prolonged periods of breastfeeding, but also perhaps to their indigenous ethnicity itself. The indigenous women of New Mexico, United States, have early liposubstitution of the breasts, compared with Hispanic and non-Hispanic white women.[19,20] Roubidoux et al. also observed lower mammographic density among indigenous women in the southwestern United States.[15] These authors also made comparisons between different ethnic groups in Alaska and observed that indigenous and Aleut women had less dense breasts than Eskimos.[21] In all of these studies, lower breast density was associated with lower incidence of breast cancer. In the present study, we confirmed this finding: the majority of the cases were indeed of non-dense breasts: the mammographic density in our study was well below what has been reported in the literature for non-indigenous populations.[22-24]

The importance of accurate determination of mammographic density was emphasized by Boyd et al.,[25] who observed a 2% increase in the relative risk of breast cancer for each 1% increase in the percentage of mammographic density. We sought to conduct an objective evaluation in the present study by scanning and capturing one of the mammographic views and determining the percentage area of fibroglandular tissue, and consequently, the mammographic density. The lower subjectivity was due to the calculation method, but the definition of the area to be calculated remained subjective, since it was demarcated using the computer mouse. In our study, when we grouped D1 + D2 as non-dense breasts and D3 + D4 as dense breasts, we had a high degree of inter-observer concordance, of 0.97 (< 0.0001). This level of concordance also resulted from the care with which the images were obtained, using the same technical process in all cases.

In this study, the association between age and mammographic density was statistically significant ($P \leq 0.001$). It has been demonstrated in the literature that breast tissue becomes replaced by fat with advancing age. Nonetheless, the mammographic density in our study was much lower than that of non-indigenous populations.[15,25-27] In our series, the frequency of non-dense breasts was 82%; and among the 69 postmenopausal women, only two (3%) had dense breasts, with an average age of 50.4 years. In non-indigenous populations in Brazil, three studies have shown that approximately 30% of women aged 50 years and over who were not using hormonal contraceptives had dense breasts.[22-24] In another Brazilian study, in which the participants had a mean age of 54 years, the frequency of observation of dense breasts was 45%.[18] In Sweden, Bergkvist et al.[28] observed that 65% of the women aged 35 years had high mammographic density and 15-20% of those aged 55 years.

Mammographic density is influenced by several factors, such as reproductive history, BMI, hormonal patterns and genetic factors.[29] In the present study, only age, menopausal status and FSH and estradiol levels were associated with mammographic density. Indigenous women with dense breasts had lower FSH levels and higher estradiol levels than those with non-dense breasts. The estradiol levels in postmenopausal women were equivalent to those observed in other studies,[29,30] which concluded that in postmenopausal women, mammographic density was inversely related to estradiol levels.

First childbirth before the age of 24 years, having more than two children and breastfeeding for more than two years are considered by many authors to be protective factors against breast cancer.[3,21,27] Reproductive behavior is quite different in indigenous populations, and this probably contributes towards creating a protective effect against breast cancer. This, together with other factors, might explain the low incidence of this disease among these women. Both in our study and in others, the number of children per indigenous woman was high, and the first delivery happened at an early age, thus resulting in many years of breastfeeding.[3,21,27,30] Parity is inversely associated with mammographic density,[31] and thus represents a protective factor against breast cancer.[32] It seems that the state of involution depends, in part, on parity: after successive pregnancies, stem cells and/or progenitor cells would accumulate in the mammary glands, and this has been observed in multiparous female mice. This is a valid hypothesis that would also explain the relationship between density and parity.[33]

Lactation has consistently been inversely correlated with the risk of breast cancer: the risk decreases by 4.3% for every 12 months of breastfeeding.[34] Currently, the relationship between breastfeeding and mammographic density is a matter of controversy, given that both positive and inverse associations have been found.[32,35-37] The women in our study nursed for a long period (mean of 12.9 years), and their breasts were predominantly non-dense, but despite this, breastfeeding was not significantly associated with mammographic density.

One limitation to consider in our study is that, due to the difficulties in conducting the study in this scenario of remote indigenous populations in the Amazon region, it was not possible to ascertain whether these participants might have any other clinical conditions, such as endocrine, hepatic or renal diseases. However, we ruled out the presence of these diseases based on data in the medical records provided by the National Health Foundation (FUNASA), which was the institution responsible for healthcare among indigenous people until 2010. The main researcher (JMS) himself analyzed data collected by FUNASA and observed that there was an electronic information system regarding indigenous people's health: Sistema de Informação da Saúde Indígena (SIASI). This was constantly updated with data from the special indigenous health districts (Distritos Especiais de Saúde Indígena, DISEIS). Full healthcare information is registered in this database, including international classification of diseases (ICD) codes, and the

information was considered to be quite reliable. Hence, it is unlikely that these women were suffering from diseases that could interfere with the results from the present study.

CONCLUSIONS

In this population of indigenous women in the municipality of Oiapoque, in the state of Amapá, Brazil, there were no cases of breast cancer and mammographic density was predominantly low. Age, menopausal status and FSH and estrogen levels were associated with mammographic density.

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Sociodemographic characteristics of women in a public hospital in Campinas who underwent legal abortion due to sexual violence: cross-sectional study

Características sociodemográficas de mulheres que realizaram aborto legal decorrente de violência sexual em um Hospital Público em Campinas: estudo transversal

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KEY WORDS:
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PALAVRAS-CHAVE:
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Estupro.

ABSTRACT

CONTEXT AND OBJECTIVE: Sexual violence is increasingly frequent worldwide. The aim here was to evaluate the sociodemographic and psychological characteristics of women who requested legal abortion, at a public healthcare service, after suffering sexual violence.

DESIGN AND SETTING: Retrospective descriptive study on 131 women who underwent legal abortion at the University of Campinas between 1994 and 2014, consequent to sexual violence.

METHODS: The sociodemographic and psychological characteristics of women who were victims of sexual violence were evaluated from their medical records. The tests used to evaluate possible associations were the chi-square and/or Fisher's exact test.

RESULTS: The women's mean age was 23 ± 9.2 years; 77.9% were white and 71.8% were single; 32.8% were students and 58.6% had employment outside of their homes. The majority reported that they did not know the aggressor (62.3%), but among the adolescents, 58% of the aggressors were known. The majority asked for abortion up to the 12th weeks of gestation (63.4%). Only 2.3% presented curettage complications. The psychological situation most frequently encountered was determined, in 34.4% of the cases before the abortion; and good in 32.8% after the abortion.

CONCLUSIONS: There was greater occurrence of sexual violence among students and women who worked outside. Among the students, most of these were adolescents and had no previous sexual life. The teenagers were raped by a known aggressor.

RESUMO

CONTEXTO E OBJETIVO: A violência sexual está cada vez mais frequente no mundo. O objetivo foi avaliar as características sociodemográficas e psicológicas das mulheres que solicitaram o aborto legal em um serviço público após violência sexual.

DESENHO DO ESTUDO E LOCAL: Estudo descritivo retrospectivo com 131 mulheres que realizaram aborto legal após violência sexual na Universidade Estadual de Campinas no período de 1994 a 2014.

MÉTODOS: Foram avaliadas as características sociodemográficas e psicológicas das mulheres vítimas de violência sexual por meio de seus prontuários. Os testes utilizados para avaliar possíveis associações foram o qui-quadrado e/ou o teste exato de Fisher.

RESULTADOS: A idade média foi de 23 ± 9,2; 77,9% eram brancas e 71,8% solteiras; 32,8% eram estudantes e 58,6% trabalham fora. A maioria relatou desconhecer o agressor (62,3%), porém entre as adolescentes, 58% dos agressores eram conhecidos. A maioria das mulheres solicitou o aborto com até 12 semanas de gestação (63,4%). Apenas 2,3% apresentaram complicações decorrentes da curetagem e a situação psicológica mais encontrada foi decidida em 34,4% no pré-aborto e bem em 32,8% dos casos no pós-aborto.

CONCLUSÕES: Houve maior ocorrência de violência sexual entre estudantes e mulheres que trabalham fora. As estudantes, na maioria, eram adolescentes sem vida sexual prévia. As adolescentes foram violentadas por agressor conhecido.

INTRODUCTION

In 1994, the Organization of American States (OAS) defined violence against women as "any gender-based act that causes death, injury, or physical, sexual or psychological suffering to women, both in public and private spheres".[1] Sexual violence is one of the oldest and bitterest expressions of gender violence and violation of human rights, sexual rights and reproductive rights.[2]

Multiple health problems resulting from sexual violence also need to be considered. These may include: physical damage, death and morbidities resulting from sexually transmitted diseases, such as HIV infection. There is also psychological damage that produces intense and devastating effects that are sometimes irreparable.[3] Pregnancy resulting from sexual violence is a complex process due to emotional, familial, social and biological impacts. This unwanted pregnancy is taken by many women to be a second form of violation and, because it becomes intolerable and impossible to maintain until the end, they resort to abortion.[4]

Abortion in cases of pregnancy due to sexual violence does not depend on judicial authorization in Brazil. A woman who has suffered sexual violence does not have any duty to report the occurrence to the police; nor is she obliged to submit a report to the police or to undergo medical-legal examination. However, she should be supported in taking appropriate police and judicial measures. Failure to take such action does not constitute a legal basis for denying abortion.[5,6]

OBJECTIVE

This study aimed to report on the physical and psychological situation of women who sought care through the Brazilian National Health System after having suffered sexual violence and become pregnant; and to characterize the care provided at a university reference service in the state of São Paulo for the practice of legal abortion.

METHODS

Design, setting and ethics

This was a retrospective descriptive study on women who underwent abortion induced due to sex violence. The abortion procedures were carried out at the University of Campinas (Universidade de Campinas, Unicamp) between January 1994 and December 2014. This study was approved by our institution's Research Ethics Committee, under number 4370353/1.

Participants

The sample size was obtained according to convenience, i.e. it comprised all women who requested abortion due to sexual violence during the study period.

Variables and statistical analysis

The variables analyzed were as follows: age (classified in three categories: up to 20 years, 21-30 years or more than 30 years), color (white, black or brown), marital status (single, married or others), religion (catholic, evangelical, spiritist or atheist), schooling (illiterate, completed elementary school or incomplete high school), monthly income (up to 5 minimum wages or more than 5 minimum wages), profession [student, employee (working outside of home) or housewife], sex life (yes or no), gestation (yes or no), parity (nulliparous or multiparous), cesarean section (yes or no), abortion (yes or no), weight (in kilograms), height (in meters), body mass index (BMI categorized as low weight < 20 kg/m^2, adequate weight 20-25 kg/m^2, overweight 25-30 kg/m^2 or obese > 30 kg/m^2), aggressor type (known or unknown), number of abusers (one, two or three), intimidation used (verbal, physical aggression or use of knives or firearm), type of relationship (vaginal or vaginal and others), injuries, police report (yes or no), associated diseases (other diseases presented by the women, such as diabetes mellitus, hypertension, heart diseases, thyroid diseases and others), gestational age (up to 12 weeks or over 12 weeks), use of emergency contraception (yes or no), length of hospital stay (in days), amount of misoprostol (number of tablets used), oxytocin use (yes or no), curettage (yes or no), post-abortion complications (yes or no) and psychological status before and after the abortion. All variables were obtained from the medical records. The psychological status was obtained through the description provided by the psychologist, who, at the end of his analysis, concluded with and described the psychological status of the woman in the medical record. This status was registered as "determined" (i.e. the woman had no psychological conflict with the decision) or "not determined" (i.e. the woman wanted the pregnancy to stop but considered that the situation was embarrassing).

The frequencies, means and standard deviations of the sociodemographic characteristics of these women were calculated. The tests used to evaluate possible associations were the chi-square and/or Fisher's exact test. SAS 9.4 was used to perform these procedures.

RESULTS

During the study period, 131 victims of sexual abuse sought termination of pregnancy at our institution. The mean age of the women was 23 ± 9.2 years, and evaluation according to age group showed that 36.6% of the women were between 10 and 20 years of age, 35.9% between 21 and 30 years and 27.5% between 31 and 41 years. Among these women, 77.6% were white, 16% brown and 6.1% black. Regarding marital status, 71.8% were single, 10.7% were married, approximately 10% were divorced and 7.3% had other marital status. Regarding religion, 48.8% were Catholic, 32.5% evangelical, 3.2% spiritist, 15.7% had no religion and for

6.1% there was no information about religion in their medical record (**Table 1**).

Considering monthly income, 76.4% of the women had a low income of up to five monthly minimum wages; regarding schooling level, 45.4% of them had attended elementary school. Regarding occupation, 32.8% were students and 58.6% had employment outside of their homes. Regarding sex life before the rape, 29.3% of the women had not started their sex life, 53.4% were nulliparous and 67.2% were not using any contraceptive method (**Table 1**).

Most of the women reported that they did not know the aggressor (62.3%). However, in the adolescent age group, 58.3% of the aggressors were known. Most of the acts of violence were perpetrated by one aggressor (93.5%). The women had more frequently been intimidated through physical aggression and verbal threat (54.9%) and only a few through personal injuries at the time of the consultation (3.1%) (**Table 2**).

Although presentation of a police report at the hospital was not mandatory, 91.6% of the women who underwent legal abortion presented this document. Chronic comorbidities, such as diabetes mellitus, systemic arterial hypertension and thyroid disease were not present in any of the women, possibly because they were young. However, 12.2% reported smoking.

Among the women who requested abortion, 63.4% were not more than 12 weeks pregnant and 36.6% were between 12 and 20 weeks pregnant. Emergency contraception was not used by 99.2%. To induce abortion, 56.5% of the women received up to 20 misoprostol tablets, and 3.8% used oxytocin in association with this.

Table 1. Percentage distribution of women who requested termination of pregnancy due to sexual violence, according to sociodemographic characteristics and antecedents

Characteristic	N	%
Color (n = 131)		
White	102	77.9
Brown	21	16.0
Black	8	6.1
Age (n = 131)		
Up to 20 years	48	36.6
21-30 years	47	35.9
> 30 years	36	27.5
Marital status (n = 131)		
Single	94	71.8
Married	14	10.7
Others	23	17.5
Religion (n = 123)		
Catholic	60	48.8
Evangelical	40	32.5
Spiritist	4	3.2
Atheist	19	15.5
Education (n = 130)		
Illiterate	2	1.6
Completed elementary school	57	43.8
Incomplete high school	71	54.6
Monthly income (n = 86)		
Up to 5 minimum wages	66	76.4
More than 5 minimum wages	20	23.6
Profession (n = 128)		
Student	42	32.8
Employee (working outside of home)	75	58.6
Housewife	11	8.6
Body mass index (n = 108)		
< 20 kg/m^2	12	11.1
20-25 kg/m^2	65	60.2
25-30 kg/m^2	24	22.2
> 30 kg/m^2	7	6.5
Previous sex life (n = 130)		
Yes	92	70.7
No	38	29.3
Pregnancy (n = 131)		
Nulliparous	70	53.4
Multiparous	61	46.6
Use of contraceptive method (n = 131)		
Yes	43	32.8
No	88	67.2

Table 2. Percentage distribution of women who requested termination of pregnancy due to sexual violence according to characteristics of violence and termination of pregnancy

Characteristic	N	%
Type of aggressor (n = 130)		
Known	49	37.7
Unknown	81	62.3
Number of aggressors (n = 131)		
One	123	93.9
Two	5	3.8
Three	3	2.3
Type of intimidation (n = 131)		
Verbal	47	35.8
Physical aggression	38	29.1
Knives	16	12.2
Firearm	30	22.9
Type of sexual intercourse (n = 127)		
Vaginal	125	98.4
Vaginal and others	2	1.6
Police report (n = 131)		
Yes	120	91.6
No	11	8.4
Gestational age (n = 131)		
Up to 12 weeks	83	63.4
Over 12 weeks	48	36.6
Emergency contraception (n = 131)		
Yes	1	0.8
No	130	99.2
Curettage complications (n = 131)		
Yes	3	2.3
No	128	97.7

Only 2.3% of the women presented complications (two cases of cervical lacerations and one of uterine perforation) due to curettage, which all the women underwent. Regarding psychological state, 34.4% of the women stated that they were committed to having a legal abortion at the time of the pre-abortion consultation and 32.8% declared themselves to be well at the time of the abortion. All the women were determined to stop the pregnancy. Of these, 34.4% did not have any psychological conflicts with the decision and therefore they were considered to be "determined" and the rest wanted to stop the pregnancy, but considered that the situation was embarrassing.

In comparing the study variables between the age groups, which were established as up to 20 years of age for adolescents and 21 years of age and over for adults, we found significant differences relating to type of aggressor, previous sex life, use of contraceptive method and occupation (**Table 3**).

DISCUSSION

At our service, over the last 20 years, 131 women discontinued their pregnancies due to sexual violence. In a service in Rio de Janeiro, 156 women terminated their pregnancies over a three-year period. In the Federal District, 21 women stopped their pregnancies between 1996 and 2001.[7]

Table 3. Characteristics of women and sexual violence according to age

	Adolescents (10-20 years old) (n = 48)		Adults (> 20 years old) (n = 83)		P
	N	%	N	%	
Occupation					
Student	35	72.9	7	8.4	< 0.0001
Working outside of home	4	8.3	50	60.2	
Others	9	18.8	26	31.4	
Previous sex life					
Yes	16	33.3	76	91.6	< 0.0001
No	31	64.6	7	8.4	
Contraception					
Yes	6	12.5	37	45.6	0.0054
No	42	87.5	44	55.4	
Aggressor					
Known	28	58.3	21	25.3	0.0001
Unknown	19	39.6	62	74.7	
Number of aggressors					
1	48	100	75	90.4	0.1033
> 1	0	0	8	9.6	
Intimidation					
Verbal	8	17	6	7.3	0.1160
Other forms	40	83	77	92.7	
Gestational age					
≤ 12 weeks	27	56.3	56	67.5	0.2450
> 12 weeks	21	43.8	27	22.5	

The characteristics of the women in the present study who experienced violence (mostly young white single childless women) were similar to those in other studies in the literature.[8-11]

In this study, the aggressor was unknown in 62.3% of the cases. However, among the adolescents, 58% of the cases of violence were committed by known aggressors. In a hospital in São Paulo, the perpetrator was unknown in most cases of violence against women, both among adolescents and among adults. Regarding the numbers of aggressors and the types of violence, that study and the present study had similar results, with predominance of violence by a single aggressor and vaginal sex as the type of violence.[12]

At our service, almost 92% of the women presented a police report, although this was not necessary for terminating a pregnancy due to sexual violence. However, most services choose to require a police report and often also a report from the Medical Legal Institute (MLI) to prove that the woman was actually raped (given that in Brazil, abortion is legal only under certain circumstances). In other words, it is assumed that women might lie and that professionals would need a guarantee that they were not being deceived, in order to provide this form of care. This is an attitude that reveals non-recognition of women as autonomous and responsible beings by professionals. It constitutes an important obstacle against caring for rape victims, who often fail to seek healthcare because they feel constrained by the requirement to firstly go and make report at a police body.[13]

In comparing the study variables between the age groups, i.e. from 10 to 20 years (taken to be adolescents) and from 21 to 41 years (taken to be adults), we found significant differences in relation to type of aggressor, previous sex life, use of contraceptive method and profession. Regarding the type of aggressor, 58% of the adolescents reported that the aggressors were known, while 75% of the adults reported that they were unknown. We believe that this difference between the types of aggressor (known or unknown) relates to the fact that adolescents are more susceptible to this type of violence, especially at the hands of aggressors who are part of their routine and exercise more control over maintaining their silence.

Regarding previous sex life, 65% of the adolescents had not had any sex life prior to the sexual violence, while 92% of adults had had sex. This difference was expected, since the group of adolescents included some very young women. We believe that the psychological impact on these young women is greater, since their first sexual experience was through violence. A study on 117 women showed that 33% of them had not started to have a sex life, and that 28.7% were aged 10-19 years.[10] According to the literature, this is a probable an aggravating factor regarding these women's sexuality, especially when this violence results in pregnancy.[14]

Regarding use of contraceptives, 87.5% of the adolescents were not using them, while 55% of the adults also were not using them. The non-use of prior contraception by these adolescents

may be explained by the fact that many had not had any previous sex life. Nonetheless, more than half of the adult women also were not using contraception. Regarding occupation, 73% of the adolescents were students and 60% of the adults had employment outside of their homes, which possibly made them more exposed to sexual violence.

One limitation of this study was the fact that these data were collected retrospectively on the basis of annotations in the subjects' medical files by different professionals and much information was unavailable due to incompleteness of the records.

A multicenter study conducted in Brazil, in which 4631 young adults aged 18-24 years were interviewed, showed that 21% of the women reported having had at least one episode of induced abortion and that 23% of the women's sexual intercourse resulted from coercion.[15] This study showed that there was a situation of vulnerability among young adult women, and that violence against these women was going unreported, thus resulting in life-threatening situations such as unsafe abortion. Women's lack of knowledge of their right to terminate pregnancy in the event that this resulted from rape ultimately violates women's sexual rights. Women sometimes only become aware of such rights in seeking healthcare services consequent to discovering their gestational state.[16]

Brazilian healthcare professionals' attitudes also contribute towards violation of these rights. They may lack training, information and knowledge about legal abortion procedures that are provided by the healthcare system. They may also fear being deceived by rape victims, whose reports of pregnancy due to rape are questioned, either for moral or religious reasons.[16-18]

Thus, we hope that these data will contribute towards expansion of policies that may provide more information to women and health professionals about legal abortion in order to try to reduce the damage suffered by these women.

CONCLUSION

There was greater occurrence of sexual violence among students and women who worked outside. Among the students, most of these were adolescents and had no previous sexual life. The teenagers were raped by a known aggressor.

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Time trends in physical activity of adult users of the Brazilian National Health System: 2010-2014. Longitudinal study

Tendência temporal da atividade física de adultos usuários do sistema público de saúde brasileiro: 2010-2014. Estudo longitudinal

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ABSTRACT

CONTEXT AND OBJECTIVE: In this longitudinal study, we aimed to describe time trends of physical activity (PA) in different domains from 2010 to 2014 among users of the Brazilian National Health System, taking into account the effects of sex, age and economic status (ES).

DESIGN AND SETTING: Longitudinal study conducted in five primary care units in Bauru (SP), Brazil.

METHODS: The sample was composed of 620 men and women who were interviewed in 2010, 2012 and 2014. The same group of researchers conducted the interviews, using the questionnaire developed by Baecke et al. Scores for occupational, exercise/sport, leisure-time/transportation and overall PA were considered in this longitudinal survey. Time trends of PA over the four years of follow-up were assessed according to sex, age and ES.

RESULTS: We found that after four years of follow-up, the reduction in overall PA (-13.6%; 95% confidence interval, CI = -11.9 to -15.3) was statistically significant. Additionally, declines in the occupational domain and exercise/sports participation were affected by age, while the reduction in overall PA was affected by sex, age and ES.

CONCLUSIONS: Overall PA decreased significantly from 2010 to 2014 among these outpatients of the Brazilian National Health System, and age and male sex were important determinants of PA in its different domains.

RESUMO

CONTEXTO E OBJETIVO: Neste estudo longitudinal, o objetivo foi descrever as tendências temporais de atividade física (AF) em diferentes domínios de 2010 a 2014 entre usuários do Sistema Único de Saúde, levando em conta o efeito do sexo, idade e condição econômica (CE).

TIPO DE ESTUDO E LOCAL: Estudo longitudinal realizado em cinco Unidades Básicas de Saúde em Bauru (SP), Brasil.

MÉTODOS: A amostra foi composta de 620 homens e mulheres que foram entrevistados em 2010, 2012 e 2014. O mesmo grupo de pesquisadores realizou as entrevistas utilizando o questionário desenvolvido por Baecke et al. Escores da AF ocupacional, exercícios/esportes, lazer/transporte e AF global foram considerados neste estudo longitudinal. Tendências temporais de AF nos quatro anos de seguimento foram avaliados de acordo com sexo, idade e CE.

RESULTADOS: Verificou-se que, após quatro anos de seguimento, a redução da AF total (-13,6%; intervalo de confiança, IC 95% = -11,9 a -15,3) foi estatisticamente significativa. Além disso, o declínio no domínio ocupacional e no exercício/participação esportiva foram afetados pela idade, enquanto a redução na AF total foi afetada pelo sexo, idade e CE.

CONCLUSÕES: A AF total diminuiu significativamente de 2010 para 2014 em pacientes ambulatoriais do Sistema Único de Saúde, e idade e sexo masculino foram importantes determinantes de AF em seus diferentes domínios.

INTRODUCTION

Development of new technologies and characteristics within the environment have continued to reduce the amount of energy expenditure on a daily basis.[1] Physical inactivity is an important risk factor for health, contributing substantially to the worldwide epidemic of non-communicable diseases (NCDs). These cause 5.3 million deaths per year[2] and lead to significant economic losses in developed and developing countries.[3-7]

An active lifestyle is important for promoting good health, and monitoring of lifestyles at population level is critical for decision-making regarding public health. Recent data show that, worldwide, one third of adults do not reach the recommended levels of physical activity (PA).[8] Additionally, data from the Global Burden of Disease (GBD) study published in 2015 found discordant trends for low physical activity according to sex, such that the overall summary exposure value for men increased by 2.4%, whereas the same indicator for women declined by 1.5%.[9]

In Brazil, a national surveillance system was implemented in 2006 to annually collect data on risk factors for non-communicable diseases, including low levels of PA.[10] This initiative should be recognized as a step forward for public health. However, its limitations, such as the facts that the survey is carried out by telephone, it only involves adults living in the state capital cities and the participants of the sample are not the same every year, need to be acknowledged.

In developing countries, most studies have a cross-sectional design or only assess total or leisure-time PA.[11-13] Therefore, they are vulnerable to missing crucial information regarding other PA domains (e.g. occupational, active transportation and sports data). Hence, longitudinal data are important for describing the patterns of habitual PA over time. These make it possible to understand the burden of physical inactivity on health outcomes.[14]

Monitoring of PA within primary care constitutes an important preventive action. This makes it possible to reach a wide portion of the overall population, thereby averting occurrences of diseases relating to physical inactivity and subsequent economic losses.[3,15-17]

OBJECTIVE

The objective of this study was to describe time trends of PA in different domains from 2010 to 2014, among users of the Brazilian National Health System, taking into account the effects of sex, age and economic status (ES).

METHODS

Sample

This longitudinal study was conducted from August 2010 to December 2014, in the city of Bauru, which has around 300,000 inhabitants and is located in the state of São Paulo, the most industrialized region of Brazil. Prior to implementation, the study was approved by the Ethics Committee of Universidade Estadual de São Paulo (UNESP), Bauru campus (procedural number 1046/46/01/10), and all participants gave written and verbal informed consent.

The sample size was estimated based on the percentage of the Brazilian population that is covered only by the Brazilian National Health System (60%).[18] The parameters used in making the estimate were: 3.8% error (arbitrary because there were no other similar studies), 5% statistical significance and 50% design effect. Therefore, at the baseline, a minimum sample size of 960 participants was estimated to be representative, i.e. at least 192 subjects in each primary healthcare unit (PHU) in Bauru.

The primary care of the Brazilian National Health System in Bauru is organized into 17 PHUs, spread out across all geographical regions of the city. To recruit participants for this longitudinal study, we stratified the metropolitan region of the city into five geographical regions in 2010. The biggest PHU of each geographical region was selected to take part in the study.

The Municipal Health Department provided lists with the names of all patients attended at these PHUs over the preceding six months. Taking these lists into account, 1,915 patients were randomly selected for telephone contact. This overall number of potential participants was estimated considering that there would be one refusal per two subjects invited to take part in the study.

During the telephone contact, the inclusion criteria were checked. Participants needed to be ≥ 50 years of age and to have lived in the area covered by that specific PHU for at least one year. Patients who fulfilled the inclusion criteria were invited to attend an interview and assessment at their own PHU.

Physical activity assessment

The same group of researchers (n = 3) conducted the interviews using the questionnaire developed by Baecke et al.,[19] at the specific BHU, in a quiet room reserved for the study. The version of the questionnaire used in this cohort study had previously been validated for use in Brazilian Portuguese.[20]

The questionnaire comprises 16 questions that are scored on a five-point Likert scale, ranging from never to very often/always. It addresses three domains of PA: occupational, leisure-time/locomotion and exercise/sport participation. The occupational domain is composed of eight questions that take into account behavior adopted during work activities, such as sitting, standing, walking, lifting heavy loads, sweating and feeling tired. The exercise/sport participation domain is composed of one question stratified into three sections that take into account the intensity, weekly duration (in hours) and previous length of practice (in months) of the activities performed by the interviewee. The leisure-time/transportation domain is composed of seven questions that take into account behavior during leisure-time/locomotion, like playing sports, watching television, walking and cycling. The PA level is

calculated by means of specific equations and is expressed as scores for each PA domain (higher score denotes higher PA). The sum of all domains constitutes the overall PA.

Changes in PA scores (considering all PA domains) from 2010 to 2014 were calculated and then expressed as z-scores. In the present study, z-scores ≤ -1.5 were treated as significant reductions in PA over the follow-up (dependent variable), and the sample was split up as ≤ -1.5 or > -1.5 for all PA domains.

Independent variables

The following data were obtained through interviews at the baseline and were structured as categorical variables:

1. Sex (male or female);
2. Age (< 65 years old or ≥ 65 years old); and
3. Economic status (ES; low or middle/high income).

The questionnaire used to estimate ES was a previously validated Brazilian questionnaire,[21] which specifies the following income groups: low (classes C, D and E, with family income of US$ 76.94-966.38 per month); and middle/high (classes B and A, with family income of US$ 1,823.33-2,703.61 per month at 3.60 currency exchange rate at the time of the study). The questionnaire estimates the income based on data about education attainment, possession of appliances and physical characteristics of the house (e.g. number of toilets).

Additionally, body mass index (BMI) was calculated using measurements of weight and height in each patient and was obtained by dividing weight by squared height (kg/m^2).

Statistical analyses

Descriptive statistics were presented as means, medians, standard deviations, interquartile ranges and 95% confidence intervals (95% CI). The effects of sex, age and ES on PA levels were assessed using analysis of variance (ANOVA) for repeated measurements. Mean values were adjusted using the covariance explained by BMI (baseline) and PHU, thus generating estimated means and standard error means. Ordinal data were expressed as percentages, while Cox regression (expressed in terms of hazard ration [HR] and its 95% CI) was used in the multivariate model adopted, to assess associations with ordinal data (reduction of PA was treated as an outcome). All multivariate models generated using Cox regression were simultaneously adjusted according to sex, age, EC, schooling and PHU. All statistical procedures were conducted using the BioEstat software, version 5.2 (BioEstat, Teffe, Amazonas, Brazil) and statistical significance was set at $P < 0.05$.

RESULTS

We called each of the 1,915 individuals identified in the PHU lists to invite them for a baseline assessment between August and December 2010; 963 (50.3%) agreed to take part in the longitudinal study. Two years after the baseline assessment (August-December 2012), we approached these subjects again. We were able to trace 802 participants: 161 subjects could not be reached or declined to participate and 25 had died. Finally, between August and December 2014, we attempted to locate all participants again and were able to interview 695 of them: 237 subjects could not be reached or declined to participate and another 34 had died. Taking all three assessment periods into account, we thus had data on 620 participants.

It should be noted that this is an ongoing cohort study, in which the main purpose is to investigate the relationship between healthcare costs at primary care level and behavioral variables (treated as independent variables). During all three years (2010, 2012 and 2014), the medical records of all participants were assessed (n = 904, excluding 59 deaths), but only the participants for whom information about PA was available at all three assessments (2010, 2012 and 2014) were included in this study (n = 620). The final sample was composed of 620 participants (454 women; 73.2%) with the three evaluations and its baseline characteristics according to sex are presented in **Table 1**.

Regarding the occupational domain, older people's PA decreased from 2010 to 2014 (HR = 2.23; 95% CI = 1.29 to 3.86; **Table 2**). Sex and ES were not associated with modification of occupational PA. Regarding exercise/sports participation, older people presented 90% less likelihood of decreasing their PA in this domain from 2010 to 2014 (HR = 0.10; 95% CI = 0.01 to 0.84; **Table 2**). On the other hand, sex and ES were not associated with PA modification in this domain. It should be noted that no independent variable was associated with modifications in the leisure-time/transportation domain.

Taking into account the overall PA score, women had 69% less chance of decreased PA from 2010 to 2014 (HR = 0.31/ 95% CI = 0.15 to 0.64; **Table 2**), while older people presented increased likelihood of reduced PA after four years of follow-up (HR = 2.23; 95% CI = 1.03 to 4.81; **Table 2**). **Figure 1** describes the overall PA during the follow-up, according to sex (**Figure 1**, Panel A), age (**Figure 1**, Panel B) and ES (**Figure 1**, Panel C). Overall PA decreased over time independently of the variables (ANOVA parameter "time"), but women (**Figure 1A**; P-value = 0.001) and younger adults (**Figure 1B**; P-value = 0.001) were more active than men and older adults. In the overall sample, after four years of follow-up, the reductions in overall PA (-13.6%; -11.9 to -15.3) and leisure-time/transportation PA (-28.3%; -26.1 to -30.5) were statistically significant, while exercise/sports participation increased (13.3%; 10.8 to 15.7) and occupational PA did not decrease significantly (-0.9%; -6.1 to +4.2).

DISCUSSION

In this four-year longitudinal study, PA among outpatients of the Brazilian National Health System showed a significant decrease over time, mostly among men and older subjects.

Regarding the occupational domain, we observed that older people decreased their PA over the years more than the younger groups, while sex and ES were not associated with significant changes. This finding was expected when considering the age range adopted in this study for the older group, which was higher than the average retirement age in Brazil (55.1 years for men and 52.2 years for women in 2010).[22] Moreover, in order to encompass retired people who maintain PA at home, in our study we also considered household activities in the occupational domain. In agreement with our findings, recent data show that the largest absolute decline in PA among Brazilians is in the occupational domain, but the largest relative decline is in domestic PA.[1] The reduction of energy expenditure in this domain is associated with increased overweight/obesity.[23] Thus, given the growth in prevalence of obesity and its associated morbidity, mortality and economic impact, remaining physically active within the occupational/domestic domain is a key factor for public health policies.

Concerning exercise/sports participation, our results showed that older adults were less likely to decrease their PA in this domain from 2010 to 2014, and no changes according to sex or ES were

Table 1. Characteristics of the sample at baseline according to sex (Bauru, SP, Brazil; n = 620)

Numerical variables	Males (n = 166)		Females (n = 454)	
	Mean ± SD	Median (IR)	Mean ± SD	Median (IR)
Age (years)	66.01 ± 9.03	64.42 (12.20)	64.18 ± 8.45	63.65 (12.50)
Body weight (kg)	79.07 ± 14.27	78.10 (18.50)	71.97 ± 15.17	70.45 (19.40)
Height (cm)	167.09 ± 7.05	166.70 (8.40)	154.12 ± 6.12	153.8 (8.50)
Body mass index (kg/m^2)	28.21 ± 4.08	27.82 (4.70)	30.28 ± 6.03	29.51 (7.10)
Economic status (score)	20.09 ± 5.63	20.00 (8.00)	17.93 ± 5.61	17.00 (7.00)
Physical activity domains (score)				
Occupational	1.75 ± 1.24	0.75 (2.13)	3.09 ± 0.83	3.25 (0.75)
Sports/exercise	1.53 ± 0.37	1.50 (0.50)	1.46 ± 0.35	1.25 (0.25)
Leisure-time/transportation	2.85 ± 0.87	3.00 (1.25)	2.85 ± 0.73	3.00 (1.00)
Overall	6.13 ± 1.64	6.00 (2.50)	7.39 ± 1.37	7.75 (1.50)
Categorical variables	**n (%)**	**% (95% CI)**	**n (%)**	**% (95% CI)**
Age				
< 65 years	84 (50.6)	50.6 (43.00 to 58.21)	254 (55.9)	55.9 (51.38 to 60.51)
≥ 65 years	82 (49.4)	49.4 (41.79 to 57.00)	200 (44.1)	44.1 (39.49 to 48.62)
Economic status				
Low	23 (13.9)	13.9 (8.60 to 19.11)	102 (22.5)	22.5 (18.63 to 26.31)
Middle/high	143 (86.1)	86.14 (80.89 to 91.40)	352 (77.5)	77.5 (73.69 to 81.37)

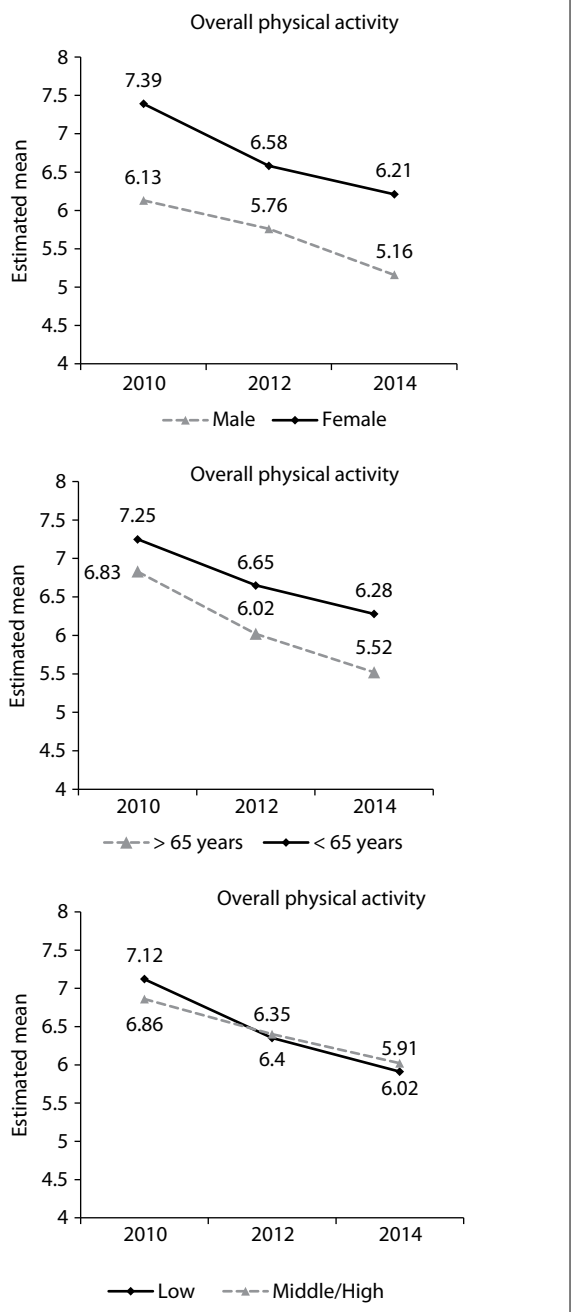
SD = standard deviation; IR = interquartile range; 95% CI = 95% confidence interval.

Table 2. Changes in physical activity from 2010 to 2014 among adults attended through the Brazilian National Health System (n = 620)

	Occupational Z-score ≤ -1.5 $HR_{adjusted}$ (95% CI)	Sports/exercise Z-score ≤ -1.5 $HR_{adjusted}$ (95% CI)	Leisure-time/transportation Z-score ≤ -1.5 $HR_{adjusted}$ (95% CI)	Overall Z-score ≤ -1.5 $HR_{adjusted}$ (95% CI)
Sex				
Male	1.00	1.00	1.00	1.00
Female	0.64 (0.37 to 1.08)	1.99 (0.43 to 9.04)	0.23 (0.03 to 1.41)	0.31 (0.15 to 0.64)
Age				
< 65 years	1.00	1.00	1.00	1.00
≥ 65 years	2.23 (1.29 to 3.86)	0.10 (0.01 to 0.84)	0.65 (0.10 to 4.05)	2.23 (1.03 to 4.81)
Economic status				
Low	1.00	1.00	1.00	1.00
Middle/high	1.19 (0.66 to 2.15)	0.42 (0.05 to 3.31)	1.10 (0.11 to 10.57)	1.52 (0.70 to 3.31)

HR = hazard ratio; 95% CI = 95% confidence interval; Cox regression simultaneously adjusted for sex, age, economic condition, primary healthcare unit and schooling.

observed. Considering the age range of the population in our study, it is reasonable to think that the older group (age ≥ 65 years old) was less likely to present modifications to their routines, mainly because most of them had already retired. Moreover, the PA scores in this domain are usually lower in older groups than in younger groups and thus less prone to modifications. Finally, in early old age (65-75 years), there may be a modest increase in physical activity, in an attempt to fill free time resulting from retirement.[24]



Notes: Estimated means = adjusted for baseline body mass index and primary healthcare unit.

Figure 1. Overall physical activity from 2010 to 2014 according to sex, age and economic status (Bauru, SP, Brazil; n = 620).

Regarding overall PA, women had 69% less chance of decreased PA from 2010 to 2014, while older people presented increased likelihood of reduced PA after four years of follow-up. In this sample, overall PA decreased by 13% during the follow-up period. In general, women spend less time doing exercise/sports activities, but the time spent doing household activities is substantially higher, which increases the overall score in comparison with men (household activities are performed daily, while exercise/sports during leisure time are not). Regarding the decline in overall PA with age, it is well established in the scientific literature that PA decreases from adolescence to adulthood,[25] and is expected to continue decreasing during the aging process. The declining trend in overall PA usually increases the percentage of body fat and reduces muscle strength, agility, flexibility and endurance, thus compromising the ability to remain physically fit.[26] However, it is well known that the prevalence and incidence of NCDs increase with age, which emphasizes the importance of becoming physically active or maintaining the existing levels of PA.

The biggest strength of our study consisted of its description of longitudinal patterns of PA in different domains according to sociodemographic characteristics. Thus, considering that one of the biggest public health challenges is to encourage individuals to be physically active, and that lifetime PA contains occupational, domestic, sports, leisure-time and transportation domains, there are many possibilities for people to reach the guideline goals of PA for health.

Nonetheless, greater availability of environments favorable for PA (which includes schools, workplaces, commuting and the built environment) is urgently needed.[27,28] Moreover, our findings indicate that development of public policies in Brazil for promoting leisure-time PA for adults and elderly people, particularly to make up for the decline of occupational PA, has not been entirely effective. This means that the amount of money that fails to be spent on public policies to promote PA might be proportional to the increase in healthcare expenditure for this population. If this indicator were to be adjusted, the country could boost its levels of total PA and, consequently, decrease the burden of undesirable health outcomes.

Some limitations should be taken into account in interpreting our results. Firstly, there are no other national studies describing time trends of PA using the same questionnaire, and therefore we were unable to make comparisons. Secondly, PA was self-reported. Although methods of greater accuracy for determining PA levels exist (and these could improve the quality of information), the costs involved and time required to conduct large studies using more direct measurement tools would be greater. Thus, use of a questionnaire

seemed more appropriate for this study. Moreover, the same staff members conducted the interviews at all stages of the analysis. Finally, we did not include any information about comorbidities.

CONCLUSIONS

In summary, overall PA decreased significantly from 2010 to 2014 among these outpatients of the Brazilian National Health System, while age and male sex were important determinants of PA in its different domains. The large decrease in overall PA (more than 10%) is of concern, especially in this specific age group, in which PA has an impact on prevention and treatment of diseases. PA decreased from 2010 to 2014 for people aged under 65 and among and women.

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Clinical characteristics of women with gestational diabetes — comparison of two cohorts enrolled 20 years apart in southern Brazil

Caraterísticas clínicas de mulheres com diabetes gestacional — uma comparação de duas coortes arroladas em intervalo de 20 anos no sul do Brasil

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KEY WORDS:
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PALAVRAS-CHAVE:
Diabetes gestacional.
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Recém-nascido.

ABSTRACT

CONTEXT AND OBJECTIVE: The prevalence and characteristics of gestational diabetes mellitus (GDM) have changed over time, reflecting the nutritional transition and changes in diagnostic criteria. We aimed to evaluate characteristics of women with GDM over a 20-year interval.

DESIGN AND SETTING: Comparison of two pregnancy cohorts enrolled in different periods, in university hospitals in Porto Alegre, Brazil: 1991 to 1993 (n = 216); and 2009 to 2013 (n = 375).

METHODS: We applied two diagnostic criteria to the cohorts: International Association of Diabetes and Pregnancy Study Groups (IADPSG)/World Health Organization (WHO); and National Institute for Health and Care Excellence (NICE). We compared maternal-fetal characteristics and outcomes between the cohorts and within each cohort.

RESULTS: The women in the 2010s cohort were older (31 ± 7 versus 30 ± 6 years), more frequently obese (29.4% versus 15.2%), with more hypertensive disorders (14.1% versus 5.6%) and at increased risk of cesarean section (adjusted relative risk 1.8; 95% confidence interval: 1.4 - 2.3), compared with those in the 1990s cohort. Neonatal outcomes such as birth weight category and hypoglycemia were similar. In the 1990s cohort, women only fulfilling IADPSG/WHO or only fulfilling NICE criteria had similar characteristics and outcomes; in the 2010s cohort, women only diagnosed through IADPSG/WHO were more frequently obese than those diagnosed only through NICE (33 ± 8 kg/m^2 versus 28 ± 6 kg/m^2; P < 0.001).

CONCLUSION: The epidemic of obesity seems to have modified the profile of women with GDM. Despite similar neonatal outcomes, there were differences in the intensity of treatment over time. The IADPSG/WHO criteria seemed to identify a profile more associated with obesity.

RESUMO

CONTEXTO E OBJETIVO: Prevalência e características do diabetes *mellitus* gestacional (DMG) modificaram-se com o tempo, refletindo transição nutricional e diferentes critérios diagnósticos. Nosso objetivo foi avaliar características de gestações com DMG em intervalo de 20 anos.

TIPO DE ESTUDO E LOCAL: Comparação de duas coortes gestacionais arroladas em diferentes períodos, em hospitais universitários de Porto Alegre, Brasil: 1991 a 1993 (n = 216) e 2009 a 2013 (n = 375).

MÉTODOS: Aplicamos dois critérios diagnósticos às coortes: International Association of Diabetes and Pregnancy Study Groups (IADPSG)/Organização Mundial de Saúde (OMS); e National Institute for Health and Care Excellence (NICE). Comparamos características e desfechos materno-fetais entre as coortes e dentro de cada uma.

RESULTADOS: Na coorte dos anos 2010, as mulheres eram mais velhas (31 ± 7 *versus* 30 ± 6 anos), obesas (29,4% *versus* 15,2%), apresentaram mais distúrbios hipertensivos (14,1% *versus* 5,6%) e risco aumentado de cesariana (risco relativo ajustado 1,8; intervalo de confiança de 95% 1,4 - 2,3), comparadas às da coorte de 1990. Desfechos neonatais, como categoria do peso ao nascer e hipoglicemia, foram semelhantes. Na coorte de 1990, essas características e desfechos foram semelhantes nas mulheres que preenchiam apenas um dos critérios; na de 2010, mulheres diagnosticadas apenas pelo IADPSG/OMS eram mais obesas (33 ± 8 kg/m^2 *versus* 28 ± 6 kg/m^2, P < 0,001) do que as diagnosticadas apenas pelo NICE.

CONCLUSÃO: A epidemia de obesidade parece ter modificado o perfil de mulheres com DMG. Embora desfechos neonatais sejam semelhantes, houve diferenças na intensidade de tratamento ao longo do tempo. O critério da IADPSG/OMS parece identificar um perfil mais associado à obesidade.

INTRODUCTION

Gestational diabetes (GDM), initially defined as the highest glycemic distribution values, has been surrounded by controversy, as detailed in the World Health Organization (WHO) position in 2013[1] and illustrated in a timeline.[2] From the 1980s to 2010, two general procedures were in vogue, one based on a 2 h/75 g oral glucose tolerance test (OGTT) with two plasma glucose values and diagnostic criteria similar to those used outside of pregnancy, and another one based on a 3 h/100 g OGTT, with four pregnancy-specific plasma glucose cutoffs.[1]

Screening for gestational diabetes in Brazil was infrequent before the 1990s, but both OGTT procedures were increasingly adopted thereafter. The 2 h/75 g OGTT gained wider acceptance after a 1997 consensus meeting[3] at which GDM was defined using the intermediate hyperglycemic cutoffs that are used outside of pregnancy (fasting ≥ 110 mg/dl; 2 h ≥ 140 mg/dl). This definition was validated using data from the Brazilian Gestational Diabetes Study (Estudo Brasileiro de Diabetes Gestacional, EBDG)[4] and remained the main diagnostic criterion used in Brazil, usually with two-step screening based on fasting values.[3]

In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) made new recommendations based on a 75 g OGTT and using data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.[1] Their recommendations have been endorsed by various entities, but new controversies arose. Perhaps the most important of these was the observed increase in GDM prevalence, especially when applied universally.[5,6]

This led other bodies to maintain the previous two-step diagnostic and screening procedures.[1] In 2013, the World Health Organization (WHO) recommended the IADPSG criteria,[1] although it warned of possible difficulties in implementing them. Alternatives to aid implementation were also proposed.[7] In 2015, the British National Institute for Health and Care Excellence (NICE)[8] made new recommendations. These are quite similar to the 1999 WHO[1] criteria for the 2 h value (140 mg/dl), but specifically define a lower fasting plasma glucose cutoff (100 mg/dl) that matches the cutoff for impaired fasting glucose established by the American Diabetes Association in 2004.[9] This strategy had been previously suggested by the Latin American Diabetes Association, in 2007,[10] and resembles the one adopted in Brazil in 1997, although at that time, it was based on the impaired fasting glucose cutoff in vogue for use outside of pregnancy (110 mg/dl). Although the 1997 diagnostic criteria are still used in Brazil, the new IADPSG/WHO criteria are increasingly being adopted. The question that arises is whether the clinical profile of women detected through the IADPSG/WHO criteria differs from the profile of those detected through the NICE criteria. Moreover, it can be asked whether these profiles have changed over time.

OBJECTIVE

The aim of the study was to evaluate changes in clinical characteristics and maternal and offspring outcomes over 20 years, between two Brazilian cohorts of women with GDM, and compare them when classified through the IADPSG/WHO or NICE criteria.

METHODS

This study is a comparison of two cohorts of pregnant women in Brazil.

We studied two cohorts of women with GDM who had singleton pregnancies and at least one prenatal appointment in two university hospitals. A 75 g OGTT with two or three glucose measurements was available for 560 (94.8%) women, while confirmatory fasting plasma glucose data was available for 31 (5.2%). We applied two recent criteria for GDM to both cohorts:

1. the IADPSG/WHO criteria: FPG ≥ 92 mg/dl or 1-h plasma glucose ≥ 180 mg/dl or 2-h plasma glucose ≥ 153 mg/dl;[1] and
2. the NICE criteria: fasting plasma glucose (FPG) ≥ 100 mg/dl or 2 h plasma glucose ≥ 140 mg/dl.[8]

The first cohort was composed of 216 women who met either of the two contemporary criteria for GDM (IADPSG/WHO or NICE). This cohort was derived from a cohort of 1031 women who were enrolled between 1991 and 1993, in general prenatal clinics of two university hospitals in Porto Alegre, which was one of the centers of the EBDG study.[4] In the original cohort, cases with known pre-gestational diabetes had been excluded at the time of booking, and only the cases that reached diabetes levels outside of pregnancy had been treated.[11]

The second cohort was recruited between November 2009 and December 2013 and was composed of 375 women who had been referred to a high-risk pregnancy prenatal clinic at a public university hospital located in the southernmost state of the country, which provides medical care through the Brazilian National Health System (Sistema Único de Saúde, SUS). In 2013, around 3,800 babies were delivered at the hospital and the cesarean rate was 35.16%.[12] All eligible women with singleton pregnancies who had a diagnosis of GDM through either of the two GDM criteria were included and cared for by a multidisciplinary team. The dietary counseling differed according to the individuals' BMI and gestational stage, and emphasized low glycemic index and carbohydrates, along with high intake of fiber-rich foods.

We collected information on sociodemographic characteristics, medical history and pregnancy outcomes. The pre-gestational weight was obtained through self-reporting. Weights and heights were measured with the subjects wearing light clothes and no shoes. Use of diets, insulin and oral medications (metformin or glyburide) were considered to be "any treatment". Data on pregnancy follow-up, delivery and maternal and newborn outcomes were retrieved from medical files.

A positive family history of diabetes was defined as among first-degree relatives, and gravidity, as the number of pregnancies including the current one. Pre-gestational BMI was calculated as the informed pre-pregnancy weight divided by the square of the height and categorized according to the current WHO classification.[13] Total weight gain was calculated as the difference between the last registered weight (measured at delivery or at the last prenatal appointment) and the informed pre-pregnancy weight. The 2009 Institute of Medicine recommendations were used to classify weight gain adequacy: for underweight women, 12.5 to 18 kg; normal BMI, 11.5 to 16 kg; overweight, 7 to 11 kg; and obese, 5 to 9 kg.[14] Hypertensive-related disorders of pregnancy were a composite of gestational hypertension, preeclampsia and eclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP).[15]

We used the Alexander birth weight chart[16] to classify newborns as small for gestational age (SGA) or as large for gestational diabetes (LGA), according to birth weight and gestational age. The latter was based on the first day of a reliable last menstrual period or on first-trimester ultrasonography. Macrosomia was defined as birth weight ≥ 4,000 g at term, and preterm birth, as delivery at less than 37 gestational weeks.[17]

The ethics committees of both hospitals approved the study protocols (number 90-058 for the 1990s cohort and number 10-0364 for the 2010s cohort). Informed consent was obtained from all individual participants included in the study.

Statistical analysis

The data are presented as means (with standard deviation) or proportions (%). Student's t test and Pearson's χ^2 test (with the Z test for comparison of proportions and Bonferroni's correction) were used to compare the two GDM groups. Kappa statistics were used to calculate the level of agreement between the two diagnostic criteria. For adjustment of outcomes, we performed Poisson regression with robust variance and, in the models, we included the mothers' baseline characteristics that were significant in univariable analyses. The outcomes assessed were: hypertensive disorders, cesarean section, preterm delivery, birth weight, frequencies of SGA and LGA, macrosomia, malformation, hypoglycemia and perinatal death. The 1990s cohort was taken to be the as reference and the results were presented as crude and adjusted relative risk (RR) and 95% confidence interval (CI). The statistical analyses were performed using the SPSS software, version 18.8. Statistical significance was set at 0.05, and was taken to be two-sided.

RESULTS

The main characteristics of the two cohorts are shown in **Table 1**. Age, schooling and gravidity were greater in the recent cohort, while living with a partner and smoking decreased, the latter in a remarkable way (33.3 to 9.6%). The nutritional characteristics also changed importantly, such that the women of the 2010s cohort were notably more obese (45.1 versus 15.2%) before becoming pregnant and reached a higher weight at delivery (86 ± 18 versus 74 ± 12 kg). Accordingly, the plasma glucose values for the 2010s cohort were higher, based on fasting, 1 h and 2 h values. Additionally, the diagnosis of GDM was reached slightly earlier for the 2010s cohort and treatment was notably more frequent. The women of the 2010s cohort reported having markedly greater family histories of diabetes and having had a previous pregnancy with GDM. Although not statistically significant, a trend towards higher frequency of chronic hypertension was also observed, with slightly higher levels of diastolic blood pressure.

As seen in **Table 2**, the women of the 2010s cohort ended their pregnancies with a slightly shorter duration and higher frequency of cesarean section. Pregnancy-related hypertension was more frequent but total gestational weight gain and adequacy of gestational weight gain did not differ much between the two cohorts. The main offspring

Table 1. Characteristics of women in two gestational diabetes cohorts*, 20 years apart

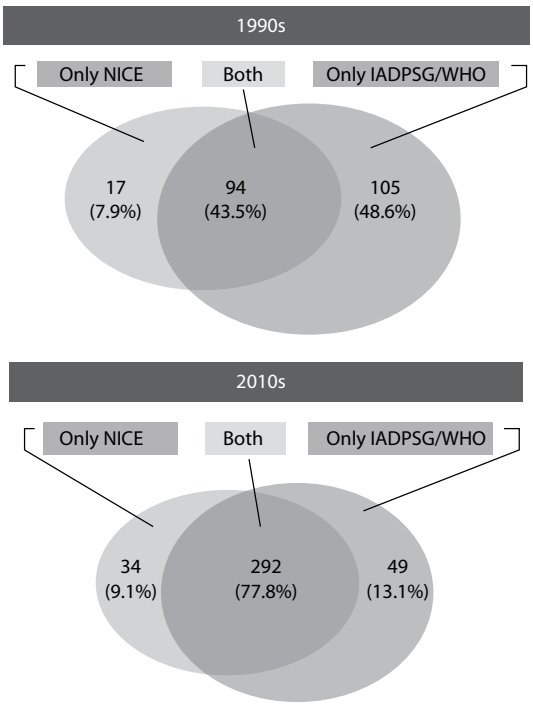
Characteristic	1990s cohort n = 216 Mean (SD) or %	2010s cohort n = 375 Mean (SD) or %	P-value†
Age (years)	30 (6)	31 (7)	0.004
White skin color (versus non-white)	71.3	74.1	0.514
Schooling (≥ 11 years)	4.2	48.3	< 0.001
Living with partner	94	61.1	< 0.001
Gravidity	2.2 (2.2)	2.7 (1.6)	0.005
Current smoking	33.3	9.6	< 0.001
Family history	16.8	51.2	< 0.001
Previous GDM	1.4	13.9	< 0.001
Pre-gestational weight (kg)	63 (11)	76 (18)	< 0.001
Pre-gestational BMI (kg/m²)	26 (4)	30 (7)	< 0.001
BMI categories (kg/m²)			
< 25‡	49.3	25.5	
25 ≤ BMI < 30	35.5	29.4	< 0.001
≥ 30	15.2	45.1	
Chronic hypertension	8.3	13.6	0.074
Systolic BP (mm/Hg)	118 ± 14	117 ± 12	0.191
Diastolic BP (mmHg)	72 (10)	73 (10)	0.154
Gestational age, diagnosis (weeks)	25 (3)	24 (6)	< 0.001
Diagnostic OGTT (mg/dl)			
Fasting	95 (9)	99 (23)	0.012
1 hour	153 (37)	180 (34)	< 0.001
2 hour	126 (3)	162 (33)	< 0.001
Any GDM treatment§	5.1	52.5	< 0.001

BMI = body mass index; BP = blood pressure; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test. *Gestational diabetes diagnosed through the criteria of either IADPSG/WHO (International Association of Diabetes and Pregnancy Study Groups/World Health Organization) or NICE (National Institute for Health and Care Excellence); †Means (with standard deviation, SD) were compared using Student's t test; proportions (%) were compared using Pearson's χ^2 test, with the Z test for proportions, adjusted using Bonferroni's correction. ‡Includes one woman with BMI < 25 kg/m² in each cohort; §Any GDM treatment: diet for the 1990s cohort and diet + oral drug or insulin for the 2010s cohort.

outcomes were similar. Although not statistically significant, perinatal mortality decreased from 33/1,000 to 18/1,000. The adjusted relative risks of the main outcomes showed that there was higher risk of cesarean section in the 2010s cohort (**Table 2**). Although the difference in gestational age at delivery was significant in univariable analyses (5 days less in the 2010s cohort), the rates of preterm delivery were similar between the cohorts (14.9 versus 16.3%; P = 0.744).

In the 1990s cohort, the NICE criteria would label 51.4% of women as having GDM, while the IADPSG/WHO criteria would label 94.5% as having GDM. In the 2010s cohort, 87.0% would meet the NICE criteria and 90.9%, the IADPSG/WHO criteria. The overall agreement between the two diagnostic criteria, examining the two cohorts together, was 68% (95% CI: 66-70%) but, as shown in **Figure 1**, the rate of agreement was greater for the 2010s cohort (43.5% in the 1990s cohort and 77.8% in the 2010s cohort). The proportion of the remaining cases that would be detected through only one of the two criteria decreased over time for those only meeting the IADPSG/WHO criteria (48.0% versus 13.1%) but not for those only meeting the NICE criteria.

We then compared the clinical characteristics and outcomes for women only meeting the NICE criteria or only meeting the IADPSG/WHO criteria for the two cohorts (**Table 3**). Although the numbers became small, it was apparent that women only meeting the IADPSG/WHO criteria had higher BMI and pre-gestational weight and showed a trend towards excessive gestational weight



NICE = National Institute for Health and Care Excellence; IADPSG/WHO = International Association of Diabetes and Pregnancy Study Groups/World Health Organization.

Figure 1. Overlap of NICE criteria and IADPSG/WHO criteria in two gestational diabetes cohorts 20 years apart

Table 2. Maternal and offspring outcomes in two gestational diabetes cohorts*, 20 years apart

Outcome	1990s cohort n = 216 Mean (SD) or %	2010s cohort n = 375 Mean (SD) or %	P-value†	RR‡ (95% CI)	aRR‡ (95% CI)
Mother					
Weight at delivery (kg)	74 (12)	86 (18)	< 0.001		
Weight gain at delivery (kg)	11 (7)	10 (8)	0.120		
Gestational age, delivery (weeks)	38.3 (2.9)	37.8 (1.4)	0.005	§	§
Weight gain					
Insufficient	34.3	37.7			
Adequate	30.5	25.1	0.366		
Excessive	35.2	37.2			
Pregnancy hypertension‖	5.6	14.1	0.002	2.5 (1.4-4.7)	1.8 (0.9-3.6)
Cesarean section‖	30.4	56.5	< 0.001	1.9 (1.5-2.3)	1.8 (1.4-2.3)
Offspring					
Birth weight (g)	3228 (615)	3242 (575)	0.774		
Birth weight classification					
SGA	10.3	8.8			
AGA	79.9	78.9	0.589		
LGA	9.8	12.3			
Macrosomia	8.4	8.3	0.951		
Malformation	3.7	2.4	0.502		
Hypoglycemia	6.5	9.7	0.239		
Perinatal death	3.3	1.8	0.432		

95% CI = 95% confidence interval; AGA = adequate for gestational age; aRR = adjusted relative risk; LGA = large for gestational age; RR = relative risk; SGA = small for gestational age. *Gestational diabetes diagnosed through the criteria of either IADPSG/WHO (International Association of Diabetes and Pregnancy Study Groups/World Health Organization) or NICE (National Institute for Health and Care Excellence). †Means (with standard deviation, SD) were compared using Student's t test; proportions (%) were compared using Pearson's χ^2 test, with the Z test for proportions, adjusted using Bonferroni's correction. ‡Poisson regression with robust variance; §See comment in Results section; ‖Adjusted for center, age, schooling, gravidity, smoking, previous gestational diabetes mellitus (GDM) and pre-gestational body mass index (BMI).

gain and delivery of heavier babies, but showed less neonatal hypoglycemia. Conversely, women only meeting the NICE criteria had higher rates of neonatal hypoglycemia. For both cohorts, the mean fasting plasma glucose was higher and the 2 h plasma glucose was lower for women who only met the IADPSG/WHO criteria.

DISCUSSION

The women in the more recent cohort of GDM were more obese, had higher plasma glucose values at diagnosis, higher frequency of pregnancy-related hypertension and higher adjusted risk of cesarean section than the previous cohort, which had been assembled about 20 years earlier. They were also more frequently treated for GDM. Newborn outcomes were similar over time, except for a downward trend in perinatal mortality. We found a very good overlap (**Figure 1**) between those diagnosed through the IADPSG/WHO and through the NICE criteria in the 2010s cohort. Women only meeting the IADPSG/WHO cutoffs showed a profile more associated with the effects of the ongoing obesity epidemic.

The differences observed between the two cohorts may reflect the nationwide public policies that have been adopted, which have resulted in better social indicators, as revealed by an increasing Human Development Index (from 0.608 in 1990 to 0.755 in 2014).[18] This attainment is reflected in the higher schooling levels, later pregnancies (surprisingly, in contrast to higher gravidity) and better health indicators (such as lower rates of smoking)[19] that have been seen in the whole Brazilian population.[18] Furthermore, implementation of a national health system,[19] which has enabled almost universal access to diagnosis and treatment for gestational diabetes, may have contributed, at least partly, to the differences found between the two cohorts.

However, the effects of the obesity epidemic have hampered these successes. Brazil moved up from 9th position, in 1975, to 5th position, in 2014, in the ranking of female obesity.[20] Maternal obesity increased remarkably, revealed here through an average pregestational weight increase of 10 kg, in just 20 years between the two GDM cohorts. On average, the women in the 1990s cohort began pregnancy within the overweight category, whereas those in the 2010s cohort did so within the obesity category. Given that maternal obesity confers important adverse outcomes for both the mother and the child, and possibly for future generations,[21] this epidemic rise in obesity threatens the progress in pregnancy outcomes that has already achieved. It also puts at risk the attainability of the goals for reducing the burden of non-communicable diseases by 2025, a challenge faced by Brazil and all other nations.

Hyperglycemia and obesity share common metabolic pathways and characteristics, and thus lead to consequences that are probably indissoluble, with additive effects on GDM outcomes.[22] It is apparent that the effects of the obesity epidemic were fully manifested in our current cohort: the women were remarkably more obese, presented pregnancy hypertension more often and were at higher risk of cesarean section. Birth weight and the large-for-gestational-age rate among the newborns did not differ between the two cohorts, perhaps because of the more widespread treatment for GDM in the recent cohort.

Table 3. Characteristics and pregnancy outcomes of two gestational diabetes cohorts defined only through the NICE criteria or only through the IADPSG/WHO criteria

Characteristic	1990s cohort			2010s cohort		
	Only NICE n = 17 (7.9)	Only IADPSG/WHO n = 105 (48.6)	P-value	Only NICE n = 34 (9.1)	Only IADPSG/WHO n = 49 (13.1)	P-value*
	Mean (SD) or %	Mean (SD) or %		Mean (SD) or %	Mean (SD) or %	
Pre-gestational BMI (kg/m^2)	23.2 (3.2)	25.5 (4.8)	0.059	28 (6)	33 (8)	< 0.001
Pre-gestational weight (kg)	57 (9)	63 (13)	0.064	68 (16)	87 (21)	< 0.001
OGTT (mg/dl)						
Fasting	83 (7)†	94 (4)‡	< 0.001	84 (6)†	94 (5)‡	< 0.001
2 hours	146 (4)§	107 (19)‖	< 0.001	146 (3)§	116 (18)‖	< 0.001
Any treatment	0	0		35.3	36.7	0.893
Insulin use	0	0		2.9	10.2	0.393
GWG category						
Insufficient	23.5	36.9		38.2	35.4	
Adequate	41.2	27.2	0.422	32.4	22.9	0.467
Excessive	35.3	35.9		29.4	41.7	
Gestational hypertension	5.9	3.8	0.534	8.8	14.3	0.515
Cesarean section	41.2	24.8	0.237	55.9	42.9	0.271
Birth weight	3412 (637)	3194 (561)	0.147	3059 (498)	3313 (504)	0.026
Newborn hypoglycemia	0	2.9	> 0.999	14.7	2.0	0.040

BMI = body mass index; GWG = gestational weight gain; IADPSG/WHO = International Association of Diabetes and Pregnancy Study Groups/World Health Organization; NICE = National Institute for Health and Care Excellence; OGTT = oral glucose tolerance test. Student's t test for glycemic cutoffs: *Means (with standard deviation, SD) were compared using Student's t test; proportions (%) were compared using Pearson's χ^2 test, with the Z test for proportions, adjusted using Bonferroni's correction; †P = 0.598; ‡P > 0.999; §P > 0.999; ‖P = 0.006.

Within this scenario, over the last few years, we have faced the challenge of adopting new diagnostic criteria, following the new recommendations from IADPSG in 2010 and WHO in 2013. Our main concern is that these criteria are likely to increase the prevalence of gestational diabetes,[23] both as a result of the epidemic of maternal obesity and as a consequence of only requiring one altered cutoff for a diagnosis of GDM. Previous estimates indicated that changing from the 1997 Brazilian criteria to the new IADPSG/WHO criteria would raise the frequency of GDM from 7.6% to 18.0%, i.e. a 2.5-fold increase.[24]

As illustrated in **Figure 1**, by applying each criterion to the diagnostic test for women with GDM, the IADPSG/WHO criteria labeled a higher number of women in both cohorts as presenting GDM, although the rate of disagreement between the two criteria was lower in the 2010s cohort (down from 56.5% to 22.2%). The rate of agreement between the two different criteria varies across studies, from 49.7%[25] or 50.6%[26] to 65.6%.[27] This partial overlap suggests that these studies probably reflect distinct GDM profiles. In one study that compared the NICE and the IADPSG/WHO criteria, 55.1% of the women with GDM would be detected by both criteria, which was lower than the overlap that we found in the 2010s cohort.[28] It is possible that differences we found for the 2010s cohort concerning maternal weight and birth weight reflected the effects of the current obesity epidemic and associated factors, particularly in relation to those only meeting the IADPSG/WHO criteria. In a recent study comparing obese women with and without GDM in the first trimester of pregnancy, obesity markers such as insulin resistance and higher BMI were more frequent in those with GDM, along with higher glucose levels. It was suggested that application of IADPSG/WHO to the DALI cohort had "identified a profile akin to the metabolic syndrome".[29] Moreover, to be worthwhile, adoption of a GDM criterion that enhances prevalence should also increase the detection rate of relevant clinical outcomes. Given the low attributable fractions relating to hyperglycemia (6.7% for large for gestational age and 3.5% for preeclampsia, based on the IADPSG/WHO criteria),[24] increased detection of relevant outcomes is likely to be small.

The main strength of our study is that it enables comparison between the features of a recent GDM cohort with those of an old one. We were able to document the important effect of the obesity epidemic over this 20-year interval. The major limitation of our study relates to the source of the cohorts: the 1990s cohort was derived from a large sample and had little intervention for treatment, and although the study was directed from university hospitals, the women were attending general prenatal care. On the other hand, for the 2010s cohort, enrollment was at a specialized clinic of a university hospital and women with greater severity of hyperglycemia may have been included. These women more frequently presented histories of family diabetes and previous GDM. This could have biased our results; nevertheless, diabetes rates are also increasing worldwide[30] and this trend could potentially explain these findings. Intensive treatment in the 2010s cohort limited interpretation of pregnancy outcomes. Finally, only a few of our cases met only one criterion or the other, which limited the extrapolation of our data. Even so, some subtle differences were revealed.

CONCLUSION

Important effects reflecting the nutritional transition over time were documented through evaluation of these two GDM cohorts separated by a 20-year interval, and some differences in applying two different GDM criteria were apparent. Women only meeting the IADPSG/WHO criteria presented pregnancy features that were often linked to obesity, while those meeting the NICE criteria presented worse neonatal outcomes, here represented by hypoglycemia. Further studies focusing on the combined effects of the obesity epidemic and hyperglycemia will help to clarify similarities and differences, and whether these are real, in the profile of pregnancies diagnosed through these two currently used GDM criteria.

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Cognitive performance of premature infants: association between bronchopulmonary dysplasia and cognitive skills. Cross-sectional study

Desempenho cognitivo de prematuros: associação da displasia broncopulmonar com as habilidades cognitivas. Estudo transversal

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KEY WORDS:
Premature birth.
Bronchopulmonary dysplasia.
Cognition.
Risk factors.

PALAVRAS-CHAVE:
Nascimento prematuro.
Displasia broncopulmonar.
Cognição.
Fatores de risco.

ABSTRACT

CONTEXT AND OBJECTIVE: Children born prematurely often have worse cognitive performance than those born at term regarding skills such as memory, attention and processing speed. Bronchopulmonary dysplasia may compromise cognitive development. The aims here were: a) To describe the cognitive performance of preterm infants with very low birth weight; b) To investigate its association with bronchopulmonary dysplasia adjusted for sociodemographic, neonatal and post-neonatal factors.

DESIGN AND SETTING: Cross-sectional study developed in a public tertiary-care hospital.

METHODS: To evaluate cognition among 112 children, we applied an intelligence scale (Wechsler scale). The average scores for children with and without bronchopulmonary dysplasia were compared across the five domains of the scale. Associations with bronchopulmonary dysplasia were investigated for domains that showed significant differences between the two groups. Associations between exposure and outcome were estimated via multivariate logistic regression.

RESULTS: There were no differences in averages for the full-scale intelligence quotient, verbal intelligence quotient, performance intelligence quotient and general language composite domains. The processing speed quotient was the only domain that presented a significant difference between the two groups (P = 0.02). Among the children with bronchopulmonary dysplasia, low full-scale intelligence quotient was observed in 28.1%. In the multivariate analysis, bronchopulmonary dysplasia (odds ratio: 3.1; 95% confidence interval: 1.1-8.7) remained associated with the outcome of processing speed quotient.

CONCLUSION: Bronchopulmonary dysplasia was an independent risk factor for alteration of the processing speed quotient.

RESUMO

CONTEXTO E OBJETIVO: Crianças nascidas prematuras com frequência apresentam pior desempenho cognitivo que as nascidas a termo em habilidades como memória, atenção, velocidade de processamento. A displasia broncopulmonar pode comprometer o desenvolvimento cognitivo. Os objetivos aqui foram: a) Descrever o desempenho cognitivo de crianças nascidas prematuras com muito baixo peso; b) Investigar sua associação com a displasia broncopulmonar ajustada para fatores sócio-demográficos, neonatais e pós-neonatais.

TIPO DE ESTUDO E LOCAL: Estudo transversal desenvolvido em hospital público de cuidados terciários.

MÉTODOS: Para a avaliação cognitiva de 112 crianças, aplicamos a escala de inteligência (Wechsler scale). Foram comparadas as médias dos escores das crianças com e sem displasia broncopulmonar nos cinco domínios da escala. A associação com a displasia broncopulmonar foi investigada para os domínios que apresentaram diferença significativa entre os dois grupos. A associação entre a exposição e o desfecho foi estimada por regressão logística multivariada.

RESULTADOS: Não houve diferença entre as médias dos domínios do quociente de inteligência total, quociente de inteligência verbal, quociente de inteligência de execução e composto de linguagem geral. O quociente de velocidade de processamento foi o único domínio que apresentou diferença significativa entre os dois grupos (P = 0,02). Entre as crianças com displasia broncopulmonar, quociente de inteligência total baixo ocorreu em 28,1%. Na análise multivariada, a displasia broncopulmonar (*odds ratio*: 3,1; intervalo de confiança: 1,1-8,7) permaneceu associada ao desfecho quociente de velocidade de processamento.

CONCLUSÃO: A displasia broncopulmonar foi um fator de risco independente para alteração no quociente de velocidade de processamento.

INTRODUCTION

Premature infants may suffer from pulmonary and brain injury, along with infections early in life, thus making them more vulnerable to neurodevelopmental abnormalities.[1] In comparison with full-term children, premature children present worse cognitive performance[1-3] in skills such as memory, attention, processing speed and representational competence.[4]

In developing children, inefficiency in acquisition of elementary skills, such as attention and processing speed, can have a significant influence on their development of other more complex skills. These elementary skills form the basis from which other cognitive abilities develop. Academic performance and cognitive skills within children's future lives are influenced by executive functions as well as processing speed. It is important to identify early problems within each of these elementary skills, so as to intervene and potentially limit more generalized cognitive deficits.[5]

In Brazil, follow-up studies on children born prematurely have been conducted.[6-11] However, little information on outcomes from children with neonatal morbidity is available, including on its repercussions on cognitive development and its associations with less favorable socioeconomic and care conditions.

Bronchopulmonary dysplasia is a chronic respiratory disease that affects children born prematurely who undergo prolonged ventilatory assistance. This condition leads to readmissions to hospital, abnormalities of motor and cognitive development and high mortality.[12-14] In a cohort of children up to eight years of age who were born with very low birth weight, those with bronchopulmonary dysplasia presented worse performance on scales evaluating intelligence.[15]

Knowledge of the areas of cognition most affected among preterm infants with bronchopulmonary dysplasia may provide parameters for early interventions that might assist them in future performance.

OBJECTIVE

The objectives of this study were: a) to evaluate the cognitive development of preterm infants with very low birth weight; and b) to compare the results from the different domains of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)[16] between patients with bronchopulmonary dysplasia and those who did not develop bronchopulmonary dysplasia during their neonatal period. We sought to determine whether bronchopulmonary dysplasia had an effect that was independent from other risk factors (sociodemographic, neonatal and post-neonatal), across the different domains of the scale.

METHODS

Study design and inclusion criteria

We conducted a cross-sectional study on a prospective cohort of very low birth weight preterm infants who were followed up at a public tertiary care unit. The criteria for including children in the study were that they needed to have been born prematurely with birth weight lower than 1500 g and gestational age less than 37 weeks, between 2004 and 2008. The participants were selected during the period of neonatal hospitalization, by a trained physician.

Patients with genetic syndromes, malformations and congenital infections, and children who did not follow the cognitive evaluation protocol on the WPPSI-III[16] scale were excluded from the study.

This study was approved by the Research Ethics Committee of the Fernandes Figueira Institute (CAAE 0005.0.008.000-06). The adults responsible for the children who were evaluated provided informed consent for participation in the research.

Main outcome evaluated

The main outcome from the study was the level of cognitive development at preschool age and the main exposure of interest was bronchopulmonary dysplasia.

After discharge from the neonatal unit, the children continued to be followed up at the Newborn Care Outpatient Clinic until reaching 11 years of age and were assessed by a pediatrician and a physiotherapist regarding their overall development. These children routinely underwent cognitive assessments over the first three years of life (Bayley scale), and at preschool age and school age on the Wechsler scale.

When they reached preschool age, they underwent a cognitive evaluation by a psychologist, who applied the WPPSI-III[16] while unaware of the children's clinical history. Thus, the evaluator was blinded regarding this exposure condition. The WPPSI-III evaluates children aged between 4 years and 7 years and 3 months. It was applied in an appropriate room, in the presence of the person in charge of the child. To undergo the test, these children needed to be in good health, without any complaints, and needed to be collaborative. The duration of the test application was approximately 60 minutes.

The WPPSI-III provides standardized scores corrected according to age. The scale evaluates cognitive functioning in five domains, of which four are specific domains: verbal intelligence quotient (IQ), performance IQ, processing speed quotient and general language composite. Together, these make up the fifth domain: the full-scale IQ. This total score is described qualitatively according to the level of performance and is classified as follows: extremely low: score below 70; borderline: between 70 and 79, average-low: between 80 and 89; average: between 90 and 109; average-high: between 110 and 119; high: between 120 and 129; and very high: 130 or more.[16]

In our study, the score was divided into two categories. Scores on the full-scale, verbal, execution, processing speed and general language composite scales of less than 80 were considered to represent "low IQ".[17] Scores in these specific domains that were greater

than or equal to 80 were considered to represent "medium/high IQ". Regarding subtests, scores below 7 were considered "low" and those greater than or equal to 7 were considered "adequate". This scale has not yet been validated for the Brazilian population, although it is widely used.

Other variables evaluated

The date of the last menstrual period or an obstetric ultrasound scan performed during the first trimester was used to estimate gestational age. In the absence of this information, the method described by Ballard et al.[18] was then applied by a pediatrician on the first day of life of the baby. Weight adequacy for gestational age was based on Alexander et al.[19]

The neonatal variables included: type of birth, sex, birth weight, adequacy of weight for gestational age, gestational age, ventilatory assistance, duration of ventilatory assistance, duration of oxygen therapy and clinical intercurrences during hospitalization (respiratory distress, septicemia, apnea, pneumonia, cerebral hemorrhage and abnormalities on cerebral ultrasound scans).

Septicemia was considered to be present in cases of positive blood culture. The degree of cerebral hemorrhage was evaluated by means of cranial ultrasonography, in accordance with the classification of Papile et al.[20] The result from the ultrasound scan that presented the highest degree of hemorrhage was used in our study. The cerebral ultrasonography was considered abnormal in the presence of at least one of the following lesions: cerebral hemorrhage, increased echo density in the periventricular white matter region, periventricular leukomalacia or ventricular dilatation. Bronchopulmonary dysplasia was defined as dependence on oxygen therapy for a period greater than or equal to 28 days.[21]

Maternal/family data were obtained through interviews with the mothers during the first consultation at the follow-up clinic and these included family income, maternal age and maternal schooling. We also collected post-neonatal data on breastfeeding, respiratory morbidity (repetitive wheezing or pneumonia or hospitalization) and whether the child had attended preschool.

Data collection began in 2004 and was completed in 2012.

Statistical analysis

We estimated a required sample size of 109 children (32 with bronchopulmonary dysplasia and 77 unexposed), based on and considering the following parameters: prevalence ratio for cognitive alteration of 2.2;[22] incidence of bronchopulmonary dysplasia of 30%; cognitive alteration of 25% in the non-exposed population;[22] significance level of 5%; and power of 80%.

We calculated the prevalence of abnormalities of cognitive development in the age group between 4 and 7 years and 3 months. To analyze the difference between the proportions, we performed the chi-square test. The differences in average cognitive scores between children exposed and not exposed to bronchopulmonary dysplasia for the five domains of the scale were then ascertained. The statistical test for average differences was Student's t test. The statistical significance level was taken to be 5%.

Multivariate analysis was performed to investigate the relationships within each domain of the cognitive scale (main outcomes) that presented significant differences between the groups exposed and not exposed to bronchopulmonary dysplasia.

Associations between the exposure variable (bronchopulmonary dysplasia) and the cognitive outcomes were estimated by odds ratios (OR) and 95% confidence intervals (95% CI) using unconditional multivariate logistic regression. The neonatal characteristics (sex, birth weight lower than 1,000 g, gestational age less than 28 weeks, type of delivery, cerebral hemorrhage, abnormal brain ultrasonography, septicemia and small for gestational age), post-neonatal characteristics (breastfeeding and attending preschool) and sociodemographic characteristics (maternal age, maternal schooling and family income) of the population were investigated as confounders.

Variables showing associations both with primary exposure (bronchopulmonary dysplasia) and with cognitive outcomes, with a significance level lower than 0.20, were considered to be potential confounding factors. Using logistic regression, we investigated variations in the magnitude of the association between bronchopulmonary dysplasia and the main outcome when adjusted for each of these study variables that had been defined as potential confounding factors in the previous stage.

The variables for which adjustment caused a change to the OR of the main exposure variable (bronchopulmonary dysplasia) that was greater than 10% were selected for inclusion in the multivariate model. The variables that, after adjustment, presented associations for which the significance level was less than 0.05 were kept in the final model. The presence of interactions between covariates and the main exposure was also investigated.

RESULTS

Our population comprised 112 children (**Figure 1**). The maternal, neonatal, post-neonatal and social characteristics of the children who complied with and did not comply with the protocol were compared, and no significant differences were found. The characteristics of the study sample and a comparison between the children who developed bronchopulmonary dysplasia and those without the disease are presented in **Table 1**.

Among the 32 children affected by bronchopulmonary dyspnea, oxygen treatment was administered to 15 of them at a corrected age of 36 weeks. Eight of the children with bronchopulmonary dysplasia received corticosteroids during the neonatal period.

The average maternal age was 27 years. Regarding socioeconomic characteristics, 27.6% of the mothers of these children had not completed elementary education and 8.9% of the families had incomes below the minimum wage.

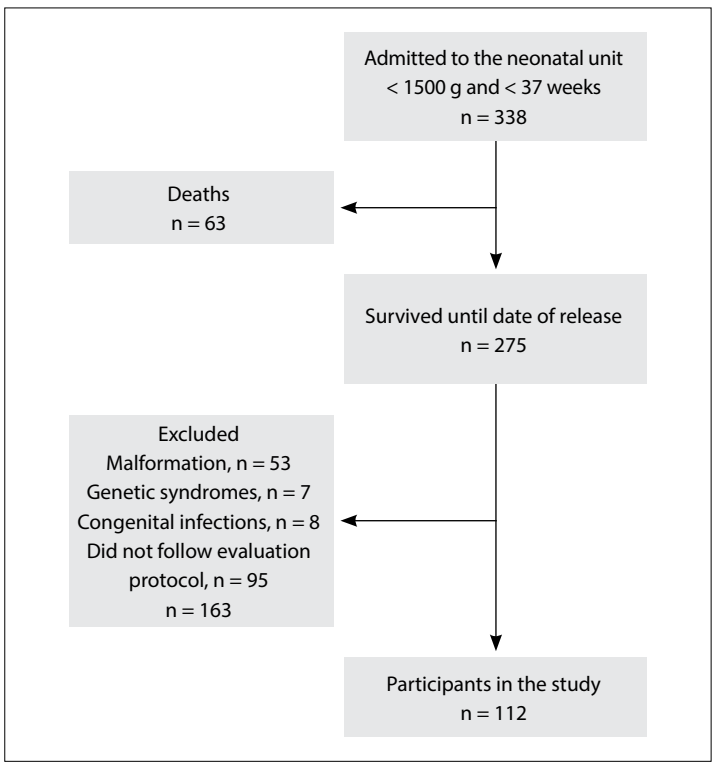

Figure 1. Flowchart of premature children involved in the study.

The frequency of respiratory morbidity up to the age of 24 months was significantly higher among the children with bronchopulmonary dysplasia (75% versus 53%). The children were breastfed for an average period of 4.4 ± 9.1 months and those with bronchopulmonary dysplasia were breastfed for a shorter period of time (1.8 ± 4.2 months) than those without the disease (5.5 ± 10.2 months) (P = 0.02).

Evaluation of cognitive development

At the time of application of the scale, the average age of the children evaluated was 5 years and 6 months (n = 112). The average full-scale IQ score was 86.8 (standard deviation, SD: 12.3); verbal IQ, 85.5 (SD 10.4); performance IQ, 92.2 (SD 13.8); processing speed quotient, 89.2 (SD 13.6); and general language composite, 89.4 (SD 14.2). We found that the average full-scale IQ and verbal IQ were close to one standard deviation from the average (85). In relation to subtests of the intelligence scale, all scores were below 10 and the subtest "matrix reasoning" was below 7.

Low full-scale IQ scores were obtained from 22.3% of the children and 5.3% had extremely low IQ. Low full-scale IQ scores was found in 28.1% of the children with bronchopulmonary dysplasia and in 20.0% of those without bronchopulmonary dysplasia. There was no significant difference between these proportions.

The average full-scale IQ was similar between children with or without bronchopulmonary dysplasia, but the average processing speed quotient was lower among the children affected by this than among those without bronchopulmonary dysplasia, as shown in the subtests that form this domain: "coding" and "symbol search",

Table 1. Characteristics of children born prematurely, with and without bronchopulmonary dysplasia

Characteristics	Total population n = 112	Bronchopulmonary dysplasia		P*
		Yes n = 32	No n = 80	
Average ± SD				
Weight at birth (g)	1133 ± 231	984 ± 190.7	1193 ± 219	0.0001
Gestational age (weeks)	29.5 ± 2	27.6 ± 1.5	30.4 ± 2.4	0.0001
Duration of ventilatory assistance (days)	3.3 ± 7.3	9.6 ± 11.0	0.8 ± 1.7	0.001
Duration of oxygen use (days)	22 ±38	63 ± 52	6 ± 7.1	0.0001
Maternal schooling level (years)	8.8 ± 2.9	8.6 ± 3.6	8.9 ± 2.7	0.56
Monthly family income (reais)	1033 ± 988	1226 ± 1308	956 ± 825	0.19
n (%)				
Male sex	51 (45.5)	20 (62.5)	31 (38.8)	0.02
Cesarean delivery	79 (70.5)	17 (53.1)	62 (77.5)	0.01
Ventilatory assistance	61 (54.5)	29 (90.6)	32 (40.0)	0.001
Neonatal pneumonia	11 (9.8)	8 (25.0)	3 (3.8)	0.002
Small for gestational age	49 (43.7)	8 (25.0)	41 (51.2)	0.01
Septicemia	13 (11.6)	9 (28.1)	4 (5)	0.001
Peri-intraventricular hemorrhage	25 (22.3)	12 (37.5)	13 (16.3)	0.01
Abnormal brain ultrasound	29 (25.9)	15 (46.9)	14 (17.5)	0.001
Preschool attendance	94 (84)	11 (34.4)	30 (37.5)	0.75

*comparison between characteristics of children with and without bronchopulmonary dysplasia.

in which the children with bronchopulmonary dysplasia had significantly worse performance (**Table 2**).

The average processing speed quotient among the children with bronchopulmonary dysplasia who underwent corticosteroid therapy during the neonatal period (n = 8) (76.6; SD: 5.5) was significantly lower than that of the children with bronchopulmonary dysplasia who did not undergo corticosteroid therapy (n = 24) (87.4; SD: 15.6).

The average scores of the children with and without bronchopulmonary dysplasia in the five domains of the cognitive scale only showed a significant difference in the domain of processing speed quotient. Therefore, associations with bronchopulmonary dysplasia at the multivariate analysis stage were only investigated for this domain.

We evaluated whether bronchopulmonary dysplasia had an effect on the outcome of processing speed quotient independently of the other factors. After adjustment for each of the confounding variables, the following variables were selected for the multivariate model: bronchopulmonary dysplasia, male sex and septicemia.

After controlling for these risk factors, male sex presented OR 2.84 (CI: 1.08-7.43), sepsis presented OR 1.26 (CI: 0.30-4.90) and bronchopulmonary dysplasia (main exposure) remained significantly (P = 0.03) associated with low processing speed quotient (OR: 3.10; CI: 1.10-8.70). No presence of any interaction between these variables and the main exposure variable was identified.

Table 2. Cognitive performance scores at preschool age among children born prematurely, with and without bronchopulmonary dysplasia

	Bronchopulmonary dysplasia		P
	Yes n = 32 mean ± SD	No n = 80 mean ± SD	
WPPSI- III scale			
Full scale IQ	86.9 [13.9]	86.8 [11.8]	0.96
Verbal IQ	86.1 [11.3]	85.2 [10.1]	0.67
Execution IQ	93.7 [15.6]	91.7 [13.0]	0.49
Processing speed quotient	84.6 [14.5]	91.0 [13.0]	0.02
General language compound	91.9 [12.9]	88.4 [14.7]	0.26
Subtests			
Block design	8.9 [3.2]	8.7 [3.2]	0.80
Coding	7.2 [3.1]	8.8 [3.3]	0.02
Information	7.6 [2.7]	7.6 [3.0]	0.98
Matrix reasoning	9.3 [3.0]	9.1 [2.7]	0.73
Picture concepts	8.9 [3.2]	8.9 [2.4]	0.99
Picture naming	8.0 [2.3]	7.5 [2.5]	0.35
Symbol search	7.0 [2.6]	8.5 [3.6]	0.03
Receptive vocabulary	9.1 [2.6]	9.2 [3.6]	0.89
Word reasoning	6.8 [2.2]	6.9 [2.6]	0.92
Vocabulary	8.2 [2.1]	8.2 [2.8]	0.97

SD = standard deviation; IQ = intelligence quotient.

DISCUSSION

Bronchopulmonary dysplasia has been shown to be an independent risk factor for cognitive alteration of skills relating to processing speed. The mechanisms that lead children with bronchopulmonary dysplasia to developmental delay are multifactorial and include chronic hypoxia and poor environmental stimulation.[13]

Bronchopulmonary dysplasia has been identified as a risk factor for several neurocognitive domains including working memory, visual-motor coordination and attention.[23] The clinical complications to which they are exposed, along with the socioeconomic vulnerability accompanying prematurity and low birth weight, predispose these children to changes in motor and cognitive development.[15]

There are few studies on the preschool and school cognition of preterm infants with very low weight belonging to Brazilian cohorts. Méio et al.[7] used the WPPSI R scale (i.e. a previous version of the scale used in the present study) and found lower IQ in the total score (75), verbal score (78.6) and performance score (77) among preterm children at the same preschool institution who were born during the preceding decade, in comparison with the results from the present study and those in the worldwide literature. Over the last decade, there have been changes in neonatal care, including decreased time spent using mechanical ventilation, which may have led to better results more recently.[24]

Espírito Santo et al.[8] found results similar to ours and reported that preschoolers born with very low birth weight had full-scale IQ, verbal and performance scores that were classified as medium-low.

Better performance was observed in the early 1990s, in a study by Anderson et al.[25] in which the Wechsler scale was applied to a cohort of extremely preterm infants who were tested at eight years of age, with an average IQ of 93. In this population of premature infants, 52% of the mothers had less than 12 years of schooling and 48% were reported as having low socioeconomic status. Gnigler et al.[23] evaluated a population of very low birth weight preterm children at the age of five years, who were born between 2003 and 2006, and obtained an average total IQ of 98.4 by means of the WPPSI- III scale.

In the present study, the average total IQ obtained through the WPPSI-III scale was 86.8 (SD: 12.3), i.e. lower than that found in the studies cited above. Moreover, almost a quarter of the total population and a third of those with bronchopulmonary dysplasia presented low IQ.

We found a high percentage of low schooling levels among the mothers of our study, such that 92% of them had attended school for less than 12 years, which may partially explain our lower cognitive outcomes. The results from more recent studies have suggested that socioeconomic factors would be more strongly associated with preschool cognition than biological factors,[2,26] and that maternal

schooling is one of the most prominent factors.[10] Although there was no difference in maternal schooling between our study groups (with and without bronchopulmonary dysplasia), the average of eight years of schooling was lower than the level reported worldwide.[25] Around 28% of the mothers in our study had not completed elementary education, which may at least partially explain the poor environmental stimulation to which these children were exposed. It is believed that greater schooling can improve professional qualifications and employment opportunities and, consequently, increase family income. In addition, higher levels of knowledge would influence child-related care practices.[27]

Performance in the "symbol search" and "coding" subtests that were used to measure the processing speed quotient was lower among the children with bronchopulmonary dysplasia. This reflected their impairments of attention, short-term memory, concentration, planning ability, motor visual coordination, motivation and learning. Higher frequencies of attention problems and learning impairment among preterm infants with bronchopulmonary dysplasia than among those without bronchopulmonary dysplasia were also shown in another study.[28]

It is noteworthy that some of the children with bronchopulmonary dysplasia in the present study had received corticosteroid therapy during the neonatal period. It has been reported that use of dexamethasone may alter the synaptic plasticity of the hippocampus and the formation of associative memory.[29] Gnigler et al.[23] found that children with bronchopulmonary dysplasia who received corticosteroid treatment were at higher risk of developing a reduction in processing speed. It is also worth mentioning that children with a history of bronchopulmonary dysplasia frequently have respiratory problems in the first years of life.[30,31] These may exacerbate their episodes of hypoxia, thereby causing repercussions relating to their future cognition and processing speed quotient. This confirms our results, since 75% of the children with bronchopulmonary dysplasia presented respiratory morbidity for up to 24 months, compared with 53% of children without the disease. In a study on the effects of perinatal risk factors on the brain structure of preterm infants, Thompson et al.[32] found that bronchopulmonary dysplasia was associated with an overall reduction of volume in the grey and white matter regions. Reductions in white matter volume may be responsible for diminishing processing speed.

In a study that made comparisons with full-term infants, preterm infants had worse outcomes in skills such as memory, processing speed, representational competence and attention, as well as lower IQ.[4] It was suggested that this difference might be represented by a model involving a cascade of effects: prematurity → elementary cognitive processes (processing speed and attention) → complex processes (memory and representational competence) → intelligence quotient.

In order to study the impact of specific neuropsychological measures on academic achievement among children who were born preterm, Mulder et al.[33] studied these children in relation to full-term controls at the ages of 9 to 10 years, with assessments that measured processing speed, executive function and IQ. They concluded that processing speed and working memory were significant predictors of overall academic achievement, such that these were important underlying factors for academic achievement among very low-weight children. They reported that all the significant differences between the groups, in terms of academic level, could be explained by processing speed. They suggested that specific rapid processing speed tests could be used as effective screening tools for assessing which children are at risk of potentially presenting educational problems and thus should be referred for complete neuropsychological evaluation. Therefore, identification of children with reduced processing speed is important in order to be able to provide special care and support, as well as to prevent further problems in school performance.[23]

Although the fact that our study population came from a single hospital may be a limitation to our study, our results are consistent with populations with similar characteristics, as described above. A larger sample size might have contributed towards a greater number of factors in the multivariate model, but the sample that was available had enough power to evaluate the association with bronchopulmonary dysplasia.

Another limitation of our study is that the Wechsler scale (WPPSI-III) has not yet been validated for the Brazilian population. Therefore, the results should be interpreted with caution, since cross-cultural adaptation issues may influence the attributes that are considered for classifying normal performance.

The present study makes a contribution towards identifying the cognitive domains that present differences between children with and without bronchopulmonary dysplasia in populations of preterm infants with very low birth weight. The difference in processing speed quotient that was obtained suggests that bronchopulmonary dysplasia may compromise this cognitive ability.

Long-term follow-up on these children, including application of neurocognitive tests, is important for identifying the children who are at risk of unsatisfactory academic performance. Moreover, knowledge of cognitive limitations provides parameters for family guidance and for pedagogical/educational interventions that may assist these children in their future lives.

CONCLUSION

This study population, from socially vulnerable families with high biological risk, presented full-scale intelligence quotient and verbal intelligence quotient within the range classified as low-average. Bronchopulmonary dysplasia was shown to be an

independent risk factor for cognitive performance, with a lower score in the dimension of the processing speed quotient.

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Physical activity in Brazil: lessons from ELSA-Brasil. Narrative review

Atividade física no Brasil: lições do ELSA-Brasil. Revisão narrativa

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KEY WORDS:
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Diabetes mellitus.

PALAVRAS-CHAVE:
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Epidemiologia.
Fatores epidemiológicos.
Hipertensão.
Diabetes mellitus.

ABSTRACT

CONTEXT AND OBJECTIVE: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) was conducted among civil servants at six higher education institutions located in six Brazilian state capitals. The objective of this review was to identify the publications produced within the scope of ELSA-Brasil that analyzed the participants' physical activity.

DESIGN AND SETTING: Review study using baseline data from ELSA-Brasil.

METHODS: Narrative review of Brazilian studies on physical activity produced using data from ELSA-Brasil participants.

RESULTS: The prevalence of leisure-time physical activity (LTPA) among ELSA-Brasil participants was low (44.1% among men and 33.8% among women). The main factors associated were social (higher schooling and family income), environmental (living in places with conditions and opportunities for physical activity) and individual (not being obese, being retired, not smoking and positive perception of body image). The perception of facilities for walking in the neighborhood was positively associated with both LTPA and commuting-related physical activity. An active lifestyle was a protective factor against several cardiometabolic variables (hypertension, diabetes, lipid abnormalities and cardiovascular risk over the next 10 years). Comparison between LTPA and commuting-related physical activity showed that only LTPA had a protective effect against arterial hypertension.

CONCLUSIONS: The prevalence of physical activity among ELSA-Brasil participants was low. The main determinants were social, environmental and personal. LTPA had a greater protective effect on cardiometabolic outcomes than did commuting-related physical activity.

RESUMO

CONTEXTO E OBJETIVO: O Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) é um estudo longitudinal com servidores públicos de seis instituições de nível superior localizadas em seis capitais brasileiras. O objetivo desta revisão foi identificar as publicações realizadas no âmbito do ELSA-Brasil que tenham analisado a atividade física dos participantes.

TIPO DE ESTUDO E LOCAL: Estudo de revisão com dados da linha de base do ELSA-Brasil.

MÉTODOS: Revisão narrativa dos estudos sobre atividade física no Brasil produzidos com dados de participantes do ELSA-Brasil.

RESULTADOS: A prevalência da atividade física no tempo livre (AFTL) em participantes do ELSA-Brasil foi baixa, (44,1% em homens e 33,8% em mulheres). Os principais fatores associados foram de ordem social (maior escolaridade e renda familiar), ambiental (viver em locais com condições e oportunidades para prática de atividade física) e individual (não ser obeso, ser aposentado/a, não ser tabagista, e ter percepção positiva da imagem corporal). A percepção de facilidades para caminhar na vizinhança foi positivamente associada tanto a AFTL quanto a atividade física no deslocamento (AFD). O estilo de vida ativo fisicamente foi fator de proteção para diversas variáveis cardiometabólicas (hipertensão arterial, diabetes, alterações lipídicas e risco cardiovascular nos próximos 10 anos). Após comparação entre AFTL e AFD, observou-se que apenas a AFTL apresenta efeito protetor para hipertensão arterial.

CONCLUSÃO: A prevalência da atividade física em participantes do ELSA-Brasil foi baixa, os principais determinantes foram de ordem social, ambiental e pessoal. A AFTL apresentou maior efeito de proteção para desfechos cardiometabólicos do que a AFD.

INTRODUCTION

At the beginnings of humankind, during the prehistoric period, people depended on their physical strength and ability to survive. They were nomads and, in their constant migrations in search of food and shelter, they made long walks along which they fought, ran and jumped. Thus, they were extremely physically active.[1] Over the centuries, humans have undergone progressive reduction in their levels of physical activity, which was accentuated by the industrial revolution and more forcefully by the current technological revolution, although this reduction varies according to culture and social class. Currently, physical activity is defined as any body movement produced by the skeletal muscles that results in energy expenditure above the levels of resting metabolism.[2] It is contextualized into four domains: leisure time, work, commuting and household-related physical activity.

For the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), it was decided to include only the domains of leisure time and commuting in the data collection. Physical activity at work and household activities were not recommended for assessment because of a tendency to overestimate the results from these domains in Latin America.[3] In addition, these domains not included in ELSA-Brasil have only shown slight associations with possible health benefits.[4-6]

Epidemiological studies on physical activity can be categorized in accordance with the model for population studies on physical activity and health proposed by Pitanga.[7] In this model, physical activity can be investigated both as a dependent variable and as an independent variable. When used as a dependent variable, the prevalence of physical activity and associated factors in population groups is studied. As an independent variable, the main consequences of physical activity are analyzed in relation to different outcomes. In the case of ELSA-Brasil, these were mainly cardiometabolic outcomes.

OBJECTIVE

The objective of this narrative review was to identify the epidemiological studies conducted within the scope of ELSA-Brasil that have analyzed the participants' physical activity both as a dependent variable and as an independent variable.

METHODS

This was a narrative review of Brazilian studies on physical activity produced using data from ELSA-Brasil participants.

What is ELSA-Brasil?

ELSA-Brasil was a cohort study on 15,105 women and men between the ages of 35 and 74 who were active or retired civil servants. They were recruited at six higher education and research institutions located in the cities of Salvador, Vitória, Belo Horizonte, Rio de Janeiro, São Paulo and Porto Alegre. The methodological details of the study have been described previously.[8,9]

Briefly, the data analyzed in the articles included in the present review were obtained at the baseline of ELSA-Brasil, between 2008 and 2010. The data had been gathered by a team of interviewers and certifiers, who had been trained and certified by a quality control committee[9] to implement the study protocol at any ELSA-Brasil Research Center. A questionnaire had been applied then by means of face-to-face interviews. The protocol for ELSA-Brasil was approved by research ethics committees at the six centers involved in the study.

Assessment of physical activity

To identify and quantify physical activity, the International Physical Activity Questionnaire (IPAQ) was used in the Elsa-Brasil. This consists of questions relating to the frequency and duration of physical activities (walking and moderate or vigorous exercise) that are developed at work, in going from place to place (commuting), in domestic activities and during leisure time.[10] In ELSA-Brasil, only the domains of leisure time and commuting were evaluated. Physical activity was measured in minutes/week by multiplying the duration of each of the activities performed by the respective weekly frequency. The prevalence of leisure-time physical activity (LTPA) stratified according to some variables analyzed in ELSA-Brasil is presented in **Table 1**.

Table 1. Prevalence of leisure-time physical activity (LTPA), stratified according to the variables analyzed in the Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010[13]

Variables	Men		Women	
Prevalence of LTPA	6788	44.1 (42.9-45.3)	8088	33.8 (32.8-34.8)
Age (years)				
34-50	3168	44.9 (42.3-47.6)	3750	31.4 (28.7-34.1)
51-59	2102	40.2 (37.1-43.8)	2619	33.5 (30.4-36.7)
≥ 60	1518	47.6 (43.8-51.2)	1719	39.7 (36.0-43.5)
Education				
Incomplete elementary	564	27.8 (21.2-35.7)	326	19.0 (10.4-31.4)
Complete elementary	569	34.4 (28.5-41.8)	444	20.7 (12.9-30.4)
High school	2221	39.8 (36.6-43.1)	2918	25.8 (22.7-29.1)
College	3434	51.2 (48.8-53.6)	4400	41.6 (39.3-43.9)
Monthly family income				
Up to 2 MW	79	32.9 (17.2-55.7)	112	19.6 (5.2-40.3)
2 MW to 8 MW	2654	35.8 (32.8-38.9)	3217	24.9 (21.9-28.0)
8 MW to 18 MW	2238	46.0 (42.9-49.1)	3069	34.7 (31.8-37.6)
Above 18 MW	1791	54.8 (51.6-57.9)	1654	50.9 (47.5-54.4)
Suitable conditions for physical activity				
No	1706	36.1 (31.3-39.0)	2281	26.0 (22.5-2973)
Yes	4703	47.5 (45.4-49.5)	5390	37.6 (35.5-39.8)
Opportunities for physical activity				
No	1659	35.5 (31.6-39.5)	1971	22.9 (19.2-27.2)
Yes	4911	47.7 (45.7-49.8)	5903	37.8 (35.8-39.9)
Functional status				
Active	5698	43.0 (41.0-45.0)	6239	31.7 (29.6-33.4)
Retired	1087	49.9 (45.6-54.2)	1844	41.3 (37.7-44.9)

MW = minimum wage.

RESULTS

Up to the present time, six papers using ELSA-Brasil baseline data that allow reflection on the main characteristics of physical activity in this population have been published. These papers deal with leisure-time and commuting-related physical activity both as dependent variables and as independent variables. In addition, another study compares the effects of leisure-time physical activity with those from commuting, with hypertension as the outcome.

Physical activity as the outcome (prevalence and associated factors)

The first study on leisure-time physical activity published within the scope of ELSA-Brasil aimed to identify the associations of body image and obesity with physical activity, and considered 13,286 participants aged 35-64 years. The main results showed that body image dissatisfaction was less likely associated with moderate physical activity among women and of vigorous physical activity among men. It was also observed that men and women with central obesity and total obesity were less likely to engage in both high and moderate-intensity physical activity. Furthermore, overweight men were more likely to engage in vigorous physical activity.[11]

Subsequently, the associations between the perceived characteristics of the neighborhood and physical activity were explored. This was a cross-sectional analysis on 14,749 ELSA-Brasil participants and the associations were tested through multinomial logistic regression. The main results observed were that the perception that the neighborhood was more walkable was positively associated with reports of participation in leisure-time physical activity, and with greater likelihood of practicing this for a longer time during the week. The perception that the neighborhood was more walkable increased the likelihood of practicing physical activity for more than 150 min/week or up to 150 min/week (in comparison with no physical activity). The perception that the neighborhood was more accessible for walking was also positively associated with active commuting (**Table 2**).[12]

Next, the prevalence and factors associated with leisure-time physical activity were identified. A hierarchical ecological model was built with the possible factors associated with LTPA grouped into blocks. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression. The prevalence of LTPA among the ELSA-Brasil participants was 44.1% among men and 33.8% among women. Among men, having a higher education level, having a higher family income, living in environments with conditions and opportunities for physical activity, being retired and being overweight were positively associated with LTPA, while current smoking, obesity and abdominal obesity were negatively associated. Among women, being over 60 years old, having a higher education level, having a higher family income, living in an environment with conditions and opportunities for physical activity and being retired were positively associated with LTPA, while being overweight or obese and having abdominal obesity were negatively associated.[13]

Table 2. Association between perceived walkability and physical activity. ELSA-Brasil, 2008-2010[12]

Variables	Better walkability
Leisure-time physical activity	
< 150	1.40 (1.28-1.52)
≥ 150	1.69 (1.57-1.83)
Commuting-related physical activity	
< 150	1.08 (0.99-1.17)
≥ 150	1.19 (1.09-1.30)

Physical activity as independent variable (cardiometabolic consequences)

In Brazil, studies on the main cardiometabolic consequences of physical activity are very important because they provide specific interpretations for the Brazilian population. Much of the existing information has been based on studies carried out abroad.

The first study published within the scope of ELSA-Brasil with physical activity as an independent variable had the main objective of identifying the association of leisure-time physical activity with cardiometabolic health. This study was developed with 10,585 participants aged 35-74, without cardiovascular diseases. Leisure-time physical activity status was defined using the American Heart Association and World Health Organization recommendations (≥ 150 min/week of moderate activity or 75 min/week of vigorous activity). After adjusting for confounding factors, the positive effects of leisure-time physical activity on cardiometabolic parameters were evident. The main results demonstrated an inverse association between leisure-time physical activity and arterial hypertension, diabetes and cardiovascular risk over the next 10 years, among both men and women[14] (**Table 3**).

Subsequently, a more recent paper aimed to assess the association of leisure-time physical activity intensity and duration with

Table 3. Association between physical activity and cardiometabolic outcomes. ELSA-Brasil, 2008-2010[14,16]

Variables	Leisure-time physical activity	Commuting-related physical activity
Hypertension		
Men	0.75 (0.65-0.87)	No associations
Women	0.78 (0.66-0.92)	1.11 (1.01-1.21)
Diabetes		
Men	0.73 (0.61-0.87)	Data unavailable
Women	0.83 (0.67-1.03)	Data unavailable
Cardiovascular diseases over next 10 years		
Men	0.67 (0.57-0.78)	Data unavailable
Women	0.78 (0.65-0.93)	Data unavailable

HDL-C, LDL-C and triglyceride levels. This was a cross-sectional study on 12,688 participants who were not on lipid-lowering medication. After adjusting for confounding factors, multiple linear regression was used to evaluate the association of intensity and duration of leisure-time physical activity with HDL-C, LDL-C and triglyceride levels. Both moderate and vigorous physical activity were found to be significantly associated with higher levels of HDL-C and lower levels of triglycerides. There were no significant associations of leisure-time physical activity with LDL-C levels.[15]

Associations of leisure-time and commuting physical activity with cardiometabolic outcomes

Finally, associations of leisure-time physical activity and commuting-related physical activity with high blood pressure were investigated among ELSA-Brasil participants. Hypertension was defined as systolic/diastolic blood pressure of > 140/90 mmHg or use of antihypertensive medications. Out of the total samples of 15,105 participants, 13,857 subjects without previous cardiovascular diseases were analyzed. The association between physical activity and hypertension was determined using Poisson regression with adjustment for confounding variables. The results showed that among both men and women, leisure-time physical activity was inversely associated with hypertension. However, in relation to commuting, the association with hypertension was positive among women and without statistical significance among men[16] (**Table 3**).

Final remarks

One possible limitation of this study is that the information on physical activity was obtained through self-reporting questionnaires. Nevertheless, these instruments are widely used in national and international studies.

The results presented here are examples of the potential for analysis of physical activity within ELSA-Brasil. This also includes the possibility that, in the near future, longitudinal data analyses may become feasible. Measurements of greater objectivity, such as accelerometry, can be expected to become incorporated, which may increase the validity of information on physical activity.

CONCLUSIONS

Through these results, it can be stated that the prevalence of leisure-time physical activity was low among ELSA-Brasil participants. This is probably reproduced in similar populations, especially those involved in academic work, and it deserves to be studied in Brazil.

The results show that different variables within the social environment (greater schooling and family income) physical setting (living in places with conditions and opportunities for physical activity) and individual sphere (obesity, being retired and smoking) present associations with physical activity. Through these results, it can also be inferred that body image and nutritional status present relationships with physical activity, for both sexes, but that the nature of the association with physical activity differs according to sex. It can also be stated that perceived walkability was independently associated with the practice of physical activity, both during leisure time and in relation to commuting.

Regarding the consequences of physical activity practices, the results confirm that leisure time physical activity was a protective factor against cardiometabolic disorders in the ELSA-Brasil cohort, both for men and for women, whereas active commuting did not have any cross-sectional association with cardiometabolic outcomes.

It can be suggested that incentive programs promoting physical activity practices should be implemented in populations similar to ELSA-Brasil that work in academic environments and are exposed to a sedentary daily life, considering that physically active behavior is a protective factor against different metabolic and cardiovascular diseases.

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Dieulafoy's disease of the bronchial tree: a case report

Doença de Dieulafoy da árvore brônquica: relato de caso

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Brônquios.
Hemoptise.
Artéria pulmonar.
Lobectomia pulmonar.

ABSTRACT

CONTEXT: Dieulafoy's disease of the bronchial tree is a very rare condition. Few cases have been reported in the literature. It can be asymptomatic or manifest with massive hemoptysis. This disease should be considered among heavy smokers when recurrent massive hemoptysis is present amid otherwise normal findings. The treatment can be arterial embolization or surgical intervention.

CASE REPORT: A 16-year-old girl was admitted to the emergency department due to hemoptysis with an unknown lesion in the bronchi. She had suffered massive hemoptysis and respiratory failure one week before admission. Fiberoptic bronchoscopy revealed a lesion in the bronchus of the right lower lobe, which was suspected to be a Dieulafoy lesion. Segmentectomy of the right lower lobe and excision of the lesion was carried out. The outcome for this patient was excellent.

CONCLUSION: Dieulafoy's disease is a rare vascular anomaly and it is extremely rare in the bronchial tree. In bronchial Dieulafoy's disease, selective embolization has been suggested as a method for cessation of bleeding. Nevertheless, standard anatomical lung resection is a safe and curative alternative.

RESUMO

CONTEXTO: A doença de Dieulafoy da árvore brônquica é uma condição muito rara, poucos casos foram descritos na literatura. Pode ser assintomática ou manifestar-se com hemoptise maciça. Esta doença deve ser considerada em fumadores pesados quando eles têm recorrentes hemoptises maciças sem outros achados anormais. O tratamento pode ser tanto embolização arterial como intervenção cirúrgica.

RELATO DE CASO: Uma menina de 16 anos foi admitida no Serviço de Urgências devido a hemoptise com uma lesão nos brônquios de origem desconhecida. Havia sofrido hemoptise maciça e insuficiência respiratória uma semana antes da admissão. A broncoscopia de fibra óptica relevou lesão no brônquio do lobo inferior direito, com suspeita de ser lesão de Dieulafoy. Foi realizada uma segmentectomia do lobo inferior direito com excisão da lesão. O resultado da paciente foi excelente.

CONCLUSÃO: A doença de Dieulafoy é uma anomalia vascular rara, sendo extremamente rara na árvore brônquica. Na doença de Dieulafoy bronquial, embolização seletiva tem sido sugerida como método para cessação do sangramento; no entanto, a habitual resseção anatômica do pulmão é uma alternativa segura e curativa.

INTRODUCTION

Dieulafoy's disease of the bronchial tree is a very rare disease. Few cases have been reported in the literature. It can be asymptomatic or can manifest with massive hemoptysis. This disease should be considered among heavy smokers with recurrent massive hemoptysis.[1]

The diagnosis can be confirmed by means of bronchoscopy, which shows aberrant arterial bleeding in the bronchial tree. Imaging, consisting of either normal chest X-ray or chest computed tomography (CT) scan, can be helpful in making the diagnosis, through ruling out other causes of hemoptysis.

The treatment usually comprises arterial embolization. If this method is unavailable or unsuccessful, surgery can be another option for achieving a definitive cure.

Here, we report a case of Dieulafoy's disease in a girl who presented with massive hemoptysis, which was diagnosed by means of bronchoscopy and treated through segmentectomy.

CASE REPORT

A 16-year-old nonsmoking girl was referred to our hospital because of an episode of massive hemoptysis. She had been admitted to a local hospital one week earlier because of this symptom and had developed respiratory failure, requiring mechanical ventilation for two days. After extubation and cessation of bleeding, she was referred to our hospital for further evaluation.

On admission to the thoracic surgery department, she was conscious and extubated, without respiratory distress, but mildly anxious. Her vital signs were stable and she was afebrile. Physical examination on the head and neck, chest, abdomen and extremities showed that these were normal. Oxygen saturation in the ambient air was 98%. There was no longer any hemoptysis.

Laboratory data including white blood cell (WBC) and platelet counts, hemoglobin and hematocrit, prothrombin time, partial thromboplastin time (PTT) and international normalized ratio (INR) were within normal limits. A chest X-ray was normal, while chest CT scans showed some patchy haziness in the right lower lobe and a very small lesion in the distal bronchus intermedius (**Figures 1** and **2**). The imaging did not show any atelectasis, honeycomb appearance, cavitation, consolidation or tumoral lesion. Common causes of massive bleeding like bronchiectasis, carcinoid tumor, tuberculosis, arteriovenous (AV) malformations and other conditions were less likely to be the reason for the bleeding in this girl.

On the next day, fiberoptic bronchoscopy was performed and this showed a lesion at the beginning of the bronchus of the basal segments of the right lower lobe, without evidence of active bleeding. The lesion originated from the mucosal surface, with a small clot over it. The mucosa surrounding the lesion was absolutely normal (**Figure 3**). No biopsy was taken, because of the suspicion of Dieulafoy's disease and the risk of bleeding. Given the lack of expertise in bronchial angiography and embolization at our center, we preferred surgical treatment. Therefore, within an elective setting and after hemorrhaging had ceased, basal segmentectomy of the right lower lobe was carried out in a planned manner, by means of right lateral thoracotomy. The superior segment of the right lower lobe remained intact (**Figure 4**). There was

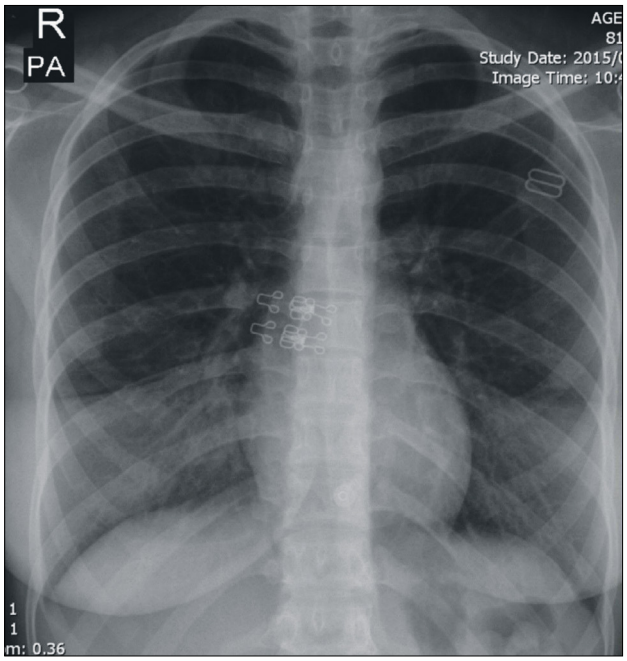

Figure 1. Chest X-ray showing nearly normal lung field.

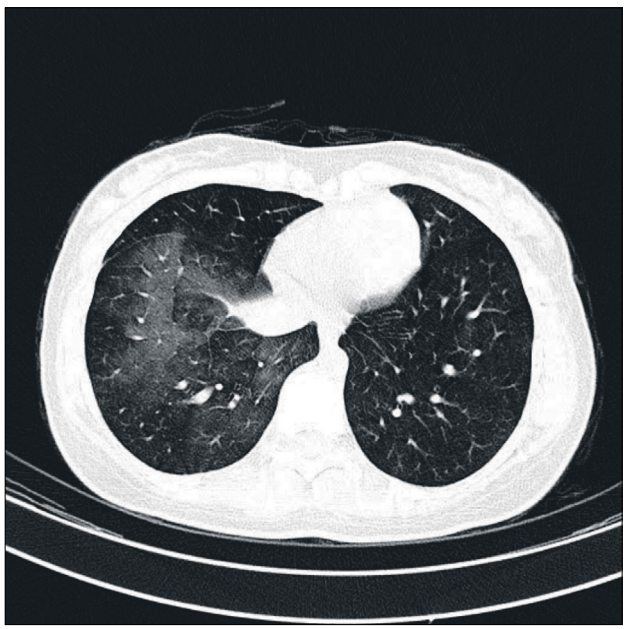

Figure 2. Computed tomography scan of the chest (pulmonary window), depicting patchy alveolar hemorrhage in right lower lobe.

no intraoperative finding except for consolidation of the parenchyma of the diseased lobe, most probably due to hemorrhage. The operation was performed without any difficulty because of normal anatomical integrity.

An intraoperative frozen section study was negative for any malignant condition.

The patient had a very smooth and uneventful postoperative course, in which she only presented pain, which could be controlled with ordinary analgesics. She was discharged on the sixth postoperative day. At an outpatient visit one week later, she did not have any serious complaint. Moreover, in the third, sixth and eighteenth months of follow-up, she was still asymptomatic without recurrence of any kind of hemoptysis.

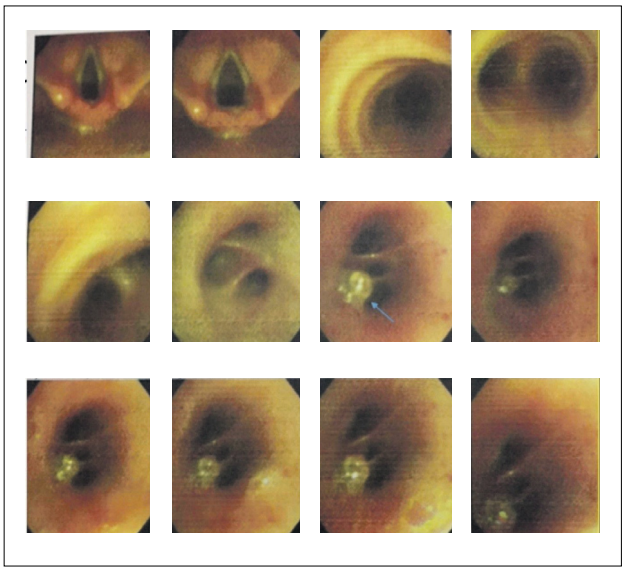

Figure 3. Bronchoscopy showing a small lesion in the bronchus of basal segments of right lower lobe (arrow).

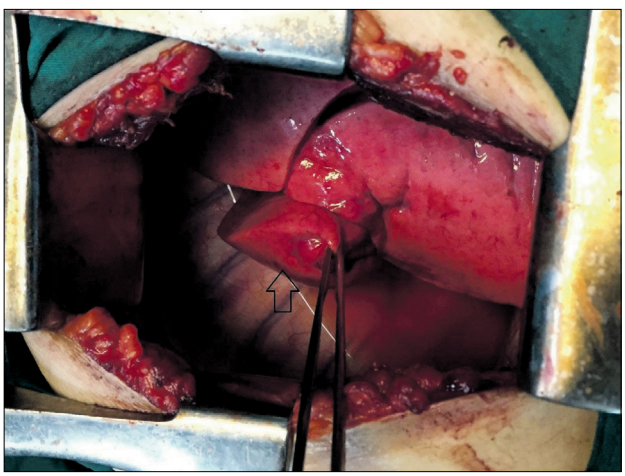

Figure 4. Right thoracic cavity after basal segmentectomy on the right lower lobe. The arrow shows upper segment of right lower lobe.

Although the diagnosis of this disease was clinical, further pathological studies showed few dilated vessels in the submucosa. This was compatible with a diagnosis of Dieulafoy's disease (**Figure 5**).

DISCUSSION

Dieulafoy's disease is a rare vascular anomaly consisting of a dysplastic artery in the submucosa. It is mostly seen in the gastrointestinal tract and is extremely rare in the bronchial tree. To the best of our knowledge, there are only a few reports of Dieulafoy's disease of the bronchial tree in the English-language literature (**Tables 1 and 2**[1-8]). Accordingly, the natural history of this disease and the preferred treatment are not known well. On the other hand, the mortality rate in the absence of any treatment rises to more than 50%.[1]

The pathogenesis of this disease is also unclear, but most reports state that it occurs in heavy smokers and presents with massive and recurrent hemoptysis. Dieulafoy's disease of the bronchus may have a congenital origin, arising from either the systemic or the pulmonary circulation.[2] Spontaneous bleeding has been described in these cases, but bleeding in such cases often occurs after a biopsy on a lesion that has not been diagnosed as a vascular anomaly. Age and tobacco use have an influence on occurrences of this disease.[1,3]

Dieulafoy's disease can be suspected when there is severe or massive hemoptysis in the absence of any significant abnormality

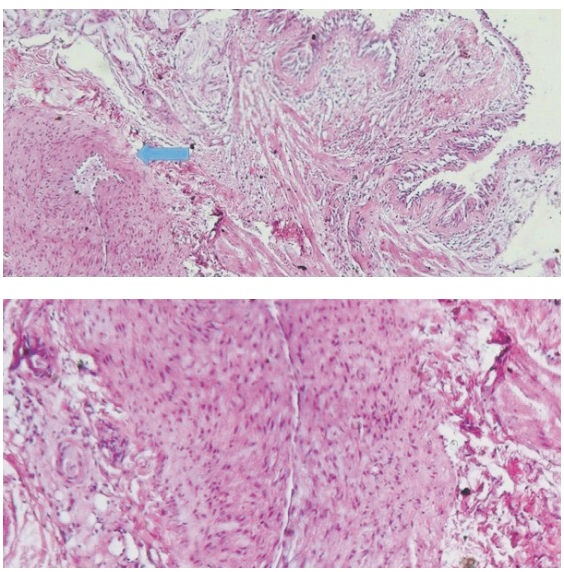

Figure 5. Histological section through bronchial Dieulafoy lesion (arrow: dilated hypertrophic submucosal artery; 2.5 X magnification, hematoxylin and eosin staining).

Table 1. Articles relating to Dieulafoy's disease that were found through searching the medical literature databases (November 22, 2016)

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed	((Dieulafoy's disease) OR Dieulafoys OR Dieulafoy)) AND (("Bronchial Diseases"[Mesh]) OR (Bronchial Disease) OR (Bronchial Disease) OR (Disease, Bronchial) OR (Diseases, Bronchial) OR (Bronchial tree) OR Bronchus) Filters: Case Reports	17	8
LILACS (via BVS)	Dieulafoy	31	0

Table 2. A review of Dieulafoy's disease reported in the medical literature

Author	Publication year	Number of patients	Location of the lesion	Treatment	Outcome
Barisione et al.[1]	2012	1	Right upper bronchus	Embolization	Successful
Bhatia et al.[5]	2003	1	Right upper segments	Recurrent embolization	Successful after three attempts
Hope-Gill and Prathibha[6]	2002	1		Embolization	Successful
Savale et al.[4]	2007	5	…	Surgery	All embolization failed; successful surgery
Fang et al.[2]	2014	1	Carina	Bilobectomy	Failed embolization; successful bilobectomy
Ganganah et al.[7]	2015	1	Right basal bronchi	Embolization	Embolization failed after three minutes; successful surgery
Smith et al.[3]	2014	1	Right lower lobe	Lobectomy	Failed embolization; successful surgical treatment
van der Werf et al.[8]	1999	1	Left upper lobe	Bronchoscopic treatment	Failed resuscitation

on either chest X-ray or chest CT scan and in the absence of any medical or surgical history, as in our patient's case. Bronchoscopy, preferably using a fiberoptic when the bleeding is not severe, may be diagnostic. It will usually make it possible to find both the source and the cause of the bleeding.[3] The characteristics of the lesion are nonspecific, but it can be suspected when a small (usually less than 1 cm) sessile non-pulsatile nodular lesion with a white cap and apparently normal mucosa is seen.[2]

It has been suggested that, after the diagnosis has been made, angiography and embolization can be the preferred treatment[5,6] and that surgical resection would only be needed in a few cases.[4] However, the failure rate of embolization is not negligible, whereas surgery alone or after failure of embolization has had a success rate of nearly 100% in all reports.[7] Nevertheless, angioembolization is less invasive than surgery, and both physicians and patients prefer it as the first attempt to halt the bleeding. In the event of surgical intervention, since the lesion is usually located in a lobar or segmental bronchus, the surgery should be carried out as an anatomical segmentectomy or lobectomy. Alternatively, bronchoplastic procedures can be performed if the lesion is located in a major bronchus. There is a lack of long-term follow-up in the reports on patients who have undergone embolization alone.[7]

Although the bleeding recurrence rate in patients whose hemorrhaging has stopped spontaneously is not known, physicians cannot take the risk of not initiating any interventions. If selective embolization is unavailable or if it fails, surgery can be lifesaving. Even in patients whose bleeding stops spontaneously, surgery can have a role in prevention of life-threatening hemoptysis.

CONCLUSION

Dieulafoy's disease is a rare vascular anomaly and is extremely rare in the bronchial tree. It should be considered as a diagnosis when there is severe or massive hemoptysis in an otherwise normal patient who has nearly normal chest imaging. Bronchoscopy is diagnostic. In bronchial Dieulafoy's disease, selective embolization has been suggested as a method for cessation of bleeding. When angioembolization fails or is unavailable, surgical resection consisting of either segmentectomy or lobectomy can be lifesaving for these patients.

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What do Cochrane systematic reviews say about the clinical effectiveness of screening and diagnostic tests for cancer?

O que as revisões sistemáticas de Cochrane falam sobre a eficácia clínica dos testes de rastreamento e diagnóstico para o câncer?

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KEY WORDS:
Diagnosis.
Early detection of cancer.
Treatment outcome.
Review [publication type].
Evidence-based practice.

PALAVRAS-CHAVE:
Diagnóstico.
Detecção precoce de câncer.
Resultado do tratamento.
Revisão.
Prática clínica baseada em evidências.

ABSTRACT

CONTEXT AND OBJECTIVE: The purpose of screening tests for cancer is to detect it at an early stage in order to increase the chances of treatment. However, their unrestrained use may lead to unnecessary examinations, overdiagnosis and higher costs. It is thus necessary to evaluate their clinical effects in terms of benefits and harm.

DESIGN AND SETTING: Review of Cochrane systematic reviews, carried out in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo.

METHODS: Cochrane reviews on the clinical effectiveness of cancer screening procedures were included. Study titles and abstracts were independently assessed by two authors. Conflicts were resolved by another two authors. Findings were summarized and discussed.

RESULTS: Seventeen reviews were selected: fifteen on screening for specific cancers (bladder, breast, colorectal, hepatic, lung, nasopharyngeal, esophageal, oral, prostate, testicular and uterine) and two others on cancer in general. The quality of evidence of the findings varied among the reviews. Only two reviews resulted in high-quality evidence: screening using low-dose computed tomography scans for high-risk individuals seems to reduce lung cancer mortality; and screening using flexible sigmoidoscopy and fecal occult blood tests seems to reduce colorectal cancer mortality.

CONCLUSION: The evidence found through Cochrane reviews did not support most of the commonly used screening tests for cancer. It is recommended that patients should be informed of the possibilities of false positives and false negatives before they undergo the tests. Further studies to fully assess the effectiveness of cancer screening tests and adverse outcomes are required.

RESUMO

CONTEXTO E OBJETIVO: O objetivo do teste de rastreamento para o câncer é detectá-lo em um estágio inicial, a fim de aumentar as chances de cura. Contudo, seu uso descomedido pode levar a exames desnecessários, sobrediagnóstico e aumento de custos. Portanto, é necessário que se avalie a repercussão clínica do rastreamento em termos de benefícios e riscos.

TIPO DE ESTUDO E LOCAL: Revisão de revisões sistemáticas Cochrane realizada na Disciplina de Medicina Baseada em Evidências da Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP).

MÉTODOS: Foram incluídas revisões sobre efetividade clínica de testes de rastreamento para câncer. Os títulos e resumos foram avaliados independentemente por dois autores e divergências foram resolvidas por outros dois. Os achados foram resumidos e discutidos.

RESULTADOS: 17 revisões sistemáticas foram incluídas: 15 sobre rastreamento para cânceres específicos (vesical, mamário, colorretal, hepático, pulmonar, nasofaríngeo, esofágico, oral, prostático, testicular, uterino) e duas para câncer em geral. A qualidade das evidências encontradas pelas revisões variou muito. Duas revisões encontraram evidências de alta qualidade: o rastreamento com tomografia em dose baixa em pacientes de alto risco parece reduzir a mortalidade por câncer pulmonar; e rastreamento com sigmoidoscopia flexível e pesquisa de sangue oculto nas fezes parece reduzir a mortalidade por câncer colorretal.

CONCLUSÃO: As evidências de revisões sistemáticas Cochrane não indicam a realização dos testes mais usados para rastreamento de câncer. Recomenda-se que os pacientes sejam informados sobre as possibilidades de falsos positivos e de falsos negativos antes de serem submetidos aos testes. Estudos adicionais para avaliar melhor a eficácia de testes de rastreamento para o câncer e os eventos adversos são necessários.

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide and was responsible for 8.8 million deaths in 2015. Its incidence is expected to increase by about 70% over the next two decades.[1] Its vast importance can be perceived from its economic impact on public health, which was estimated as US$ 1.16 trillion in 2010.[2]

Screening tests are one of the main pillars of early detection. They are performed on healthy individuals presenting different levels of risk, with the aim of detecting the disease at an early stage, even before any symptom becomes noticeable. However, carrying out these tests within screening-based programs is only justified if they lead to better health outcomes than would be achieved by treating diseases at a later stage.[3] Theoretically, the aim in performing such tests is to minimize the number of people with the disease who pass through them undetected (high sensitivity), while also minimizing the number of people without cancer who are selected for further examination (high specificity).[4]

The first concept that needs to be underscored in making a decision to implement screening is overdiagnosis. This is epidemiologically defined as a situation of diagnosing a condition that during the patient's lifetime would have remained indolent if left undetected.[5] The main consequence from this would be overtreatment, which would have no benefits for the patients, might cause harm and possibly would generate costs. Additionally, it could divert healthcare professionals and resources away from the most severely ill patients.[5] One well-known example of overdiagnosis took place during the 1950s in the United States, when breast self-examination (BSE) was widely advocated, only for it to be concluded in the 1990s that BSE had no impact on reducing breast cancer mortality.[6]

A second important concept to have in mind is the likelihood of false-negative results. Aside from the delay in detection of the disease and its further development, such situations could lead to legal action from patients affected by them, and more importantly, could reduce public confidence in screening policies.[7]

Another important aspect of screening programs to be taken into consideration is that the likelihood that a positive test will give a correct result (positive predictive value) is strongly dependent on the prevalence of the disease within the population. Hence, the effectiveness of screening programs varies between different regions. Furthermore, the effectiveness of screening tests is also affected by other variables such as adequate infrastructure, resources and professional qualification.[4] For example, although magnetic resonance imaging may have higher efficacy for detection of breast cancer, compared with conventional mammography, the infrastructure cost and the high number of false-positive results considerably increases its costs and harm, thus leading to a preference for conventional mammography.[8]

Finally, screening strategies should be implemented only in settings in which further investigation and treatment are warranted for all individuals, whenever necessary. Otherwise, there is no benefit even for evidence-based screening protocols.

OBJECTIVE

The objective of this study was to summarize the evidence from Cochrane systematic reviews regarding the clinical effectiveness of screening tests for detection of different types of cancer.

METHODS

Design and setting

This was a review of Cochrane systematic reviews carried out in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina — Universidade Federal de São Paulo (EPM-Unifesp). This article was specifically developed for the section "Cochrane Highlights", which is an initiative for disseminating Cochrane reviews. This initiative resulted from a formal partnership between the São Paulo Medical Journal and the Cochrane Collaboration, and it is supported by Cochrane Brazil.

Criteria for including reviews

- Types of studies
  Only Cochrane systematic reviews on effectiveness and safety, including randomized, quasi-randomized or non-randomized clinical trials as primary studies, were used in producing the present review. Systematic reviews focusing on diagnostic accuracy were excluded. Protocols, withdrawn reviews and previous versions of updated reviews were not taken into consideration.
- Types of participants
  All types of participants, regardless of sex and age or other characteristics (i.e. different risks for cancer, genetic factors, previous cancer), were included.
- Types of intervention
  Any screening approaches for cancer detection were included.
- Type of outcomes
  Clinical outcomes involving morbidity and mortality were considered.

Search for reviews

We developed and applied a systematic search strategy in the Cochrane Library on December 19, 2016 (**Table 1).** Two researchers

Table 1. Search strategy in Cochrane Library. December 19, 2016

#1 "Screening" in title, abstract, keywords
#2 "Mass Screening" in title, abstract, keywords
#3 "Early Detection of Cancer" in title, abstract, keywords
#4 " Screen test" in title, abstract, keywords
#5 "Screen" in title, abstract, keywords
#¨6 #1 OR #2 OR #3 OR #4 OR #5
#7 #¨6 in Cochrane Reviews

(ATPB and VLC) selected and assessed systematic reviews with themes that showed a correlation with the goals of this review. A third researcher (RR or RLP) resolved any conflicts that arose, when necessary.

RESULTS

Search results

The search resulted in 927 Cochrane systematic reviews. After the titles and abstracts had been screened, 17 reviews were found to be related to the theme and fulfilled our inclusion criteria.[9-25] Among these, 7 reviews assessed a screening method only for the general population, 7 only for a specific subpopulation and 3 for both. The reviews assessed screening approaches for the following types of cancer: cancer in general (n = 2), bladder (n = 1), breast (n = 4), colorectal (n = 2), hepatic (n = 1), lung (n = 1), nasopharyngeal (n = 1), esophageal (n = 1), oral (n = 1), prostate (n = 1), testicular (n = 1) and uterine (n = 1).

Results from systematic reviews

The 17 systematic reviews are presented below. Additionally, for those that included at least one primary study, a brief summary is then presented. The issues addressed, the main findings from each screening approach and the quality of the evidence (based on the GRADE approach[26]) are presented in **Table 2.**

Table 2. Issues addressed, main findings and quality of evidence from systematic reviews that included at least one randomized clinical trial

Type of cancer	Screening methods	Population (n)	Design of studies included	Benefits and harm	Quality of evidence (GRADE approach*)
Hepatocellular carcinoma	Alpha-fetoprotein and/or liver ultrasonography versus no screening[18]	Individuals with chronic hepatitis B	RCT (3)	There is no evidence to support or refute the use of alpha-fetoprotein.	Not assessed
Lung cancer	More frequent chest x-ray screening versus less frequent chest x-ray screening[19]	General population	RCT (8) Controlled trial (1)	No reduction of lung cancer mortality. No reduction of all-cause mortality.	Low to moderate
	Annual chest x-ray versus no regular screening[19]	General population		No reduction of lung cancer mortality after 6 and 13 years of follow-up. No reduction of all-cause mortality.	High
	Annual chest x-ray plus four-monthly sputum cytological tests versus annual chest x-ray alone[19]	General population		Chest x-ray plus sputum cytological tests do not reduce lung cancer mortality or all-cause mortality, and do not increase lung cancer 5-year survival.	Moderate to high
	Annual low-dose CT versus annual chest x-ray[19]	High-risk individuals (aged 55 to 74 years with 30 pack-years or more of smoking, or who quitted 15 years or less prior to enrolment if ex-smokers)		Low-dose computed tomography seems to reduce lung cancer mortality. Low-dose computed tomography does not seem to reduce all-cause mortality.	High
Colorectal cancer	Fecal occult blood screening versus no screening[16]	General population	RCT (4)	Screening seems to reduce colorectal cancer mortality. It is possible that screening reduces colorectal cancer incidence.	Not assessed
	Flexible sigmoidoscopy and fecal occult blood test[17]	General population	RCT (9)	Screening with both flexible sigmoidoscopy and fecal occult blood testing seems to reduce colorectal cancer mortality. Screening with flexible sigmoidoscopy seems to reduce colorectal cancer incidence. Screening with fecal occult blood testing does not seem to reduce colorectal cancer incidence.	Moderate to high

Continue...

Table 2. Continuation.

Type of cancer	Screening methods	Population (n)	Design of studies included	Benefits and harm	Quality of evidence (GRADE approach*)
Cancer (overall)	General health checkup versus no checkup[9]	General population	RCT (16)	No reduction of cancer mortality.	High
	General tests for cancer versus no test[10]	Individuals with unprovoked VTE	RCT (2)	General tests seem to lead to earlier diagnosis of cancer at an earlier stage of the disease. Insufficient evidence about cancer-related and VTE-related mortality.	Not assessed
Prostate cancer	PSA testing with or without digital rectal examination versus no screening[23]	General male population	RCT (5)	PSA does not seem to reduce mortality PSA seems to increase the diagnosing of prostate cancer and localized prostate cancer and seems to reduce the diagnosing of advanced prostate cancer.	Low to moderate
Oral cancer	Visual examination versus no examination[22]	Adults > 35 years old	RCT (1)	Visual examination does not seem to reduce mortality.	Not assessed
		High-risk individuals, > 35 years old, who used tobacco or alcohol or both		Visual examination seems to reduce oral cancer mortality, to improve survival and to reduce the number of individuals diagnosed with oral cancer of stage III or worse.	Not assessed
Breast cancer	Intensive follow-up (more intensive scheme with radiological and laboratory tests) *versus* non-intensive follow-up (regular physical examinations and yearly mammography alone)[12]	Women treated for stage 1, 2 or 3 breast cancer	RCT (5)	Intensive follow-up seems do not increase overall survival. Intensive follow-up does not seem to increase disease-free survival. Intensive follow-up does not seem to increase quality of life.	Low to high
	Centralized follow-up (by a hospital-based specialist) versus decentralized follow-up (by general practitioners)[12]	Women treated for stage 1, 2 or 3 breast cancer		Centralized follow-up does not seem to increase overall survival. Centralized follow-up does not seem to increase disease-free survival. Centralized follow-up does not seem to increase quality of life.	Moderate to high
	Regular breast self-examination versus no regular breast self-examination[14]	General female population	RCT (3)	Regular self-examination does not reduce breast cancer mortality. Regular self-examination doubled the number of biopsies with benign results.	Not assessed
	Mammography screening versus no mammography screening[15]	Women aged from 39 to 74 years	RCT (8)	Screening does not seem to reduce breast cancer mortality after 10 and 13 years (including only good-quality studies) Screening does not seem to reduce all-cancer mortality after 13 and years (including only good-quality studies) Screening seems to increase the numbers of lumpectomies and mastectomies and use of radiotherapy. Screening does not seem to change the use of chemotherapy.	Not assessed

RCT = randomized controlled trial; *GRADE = Grading of Recommendations Assessment, Development and Evaluation;[26] VTE = venous thromboembolism; PSA = prostate-specific antigen.

General health checkup among adults

The purpose of general health checkups is to detect disease and risk factors for disease with the aim of reducing morbidity and mortality. In this review,[9] the authors aimed to quantify the benefits and harm of general health checkups with an emphasis on patient-relevant outcomes such as morbidity and mortality. The results showed that there was no difference between the checkup and 'no checkup' groups regarding cancer-related mortality (risk ratio [RR] 1.02; 95% confidence interval [95% CI] 0.92 to 1.12; eight randomized clinical trials [RCTs]; 139,290 participants; 3663 deaths). The authors concluded that general health checkups did not reduce cancer-related morbidity or mortality, but that the number of new diagnoses increased. Important harmful outcomes, such as the number of follow-up diagnostic procedures or short term psychological effects, were often not studied or reported and many trials had methodological problems. With the large number of participants and deaths included and the long follow-up periods used, and considering that cancer mortality was not reduced, general health checkups are unlikely to be beneficial. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009009.pub2/full.

Tests for cancer in patients with unprovoked venous thromboembolism

An unprovoked venous thromboembolism (VTE) is one that affects patients with no underlying or immediately predisposing risk factors. It can frequently be the first clinical manifestation of an underlying malignancy. This raises the question of whether patients with an unprovoked VTE should be investigated for an underlying cancer. The treatment for VTE differs between cancer and non-cancer patients, and a correct diagnosis would ensure that patients received optimal treatment for VTE, to prevent recurrence and further morbidity. The objectives of this review[10] were to determine whether cancer testing for patients with a first episode of unprovoked VTE is effective in reducing cancer and VTE-related mortality and morbidity and to establish which tests for cancer are most useful. Two RCTs (396 patients) assessed the effect of routine cancer tests versus clinically indicated cancer tests for patients with an unprovoked VTE. Cancer-related mortality did not differ between the two testing approaches (odds ratio [OR] 0.49; 95% CI 0.15 to 1.67; P = 0.26; moderate quality evidence). Neither of the studies measured all-cause mortality, VTE-related morbidity and mortality, adverse events, or patient satisfaction. The authors concluded that there was currently insufficient evidence for firm conclusions regarding the effectiveness of cancer testing for a first episode of unprovoked VTE. The results were imprecise and could be consistent with either harm or benefit. Further good-quality RCTs are needed before definitive conclusions can be reached. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010837.pub2/full.

Follow-up strategies for women treated for early breast cancer

Follow-up examinations are often used, after primary treatment for women with breast cancer, to detect recurrences at an early (asymptomatic) stage. The objective of this systematic review[12] was to evaluate the effectiveness of different follow-up strategies for detecting distant metastasis, regarding mortality, morbidity and quality of life among women who had been treated for stage 1, 2 or 3 breast cancer. This updated review included five RCTs involving 4,023 women with breast cancer (clinical stage 1, 2 or 3). Two trials involving 2,563 women compared follow-up based on clinical visits and mammography with a more intensive scheme including radiological and laboratory tests. The data showed that there were no significant differences between the two strategies in relation to the following outcomes:

- Overall survival (hazard ratio [HR] 0.98; 95% CI 0.84 to 1.15; two RCTs; 2,563 participants; high-quality evidence);
- Disease-free survival (HR 0.84; 95% CI 0.71 to 1.00; two RCTs; 2,563 participants; low-quality evidence);
- Quality-of-life measurements (one RCT; 639 participants; high-quality evidence).

The results from subgroup analyses according to patient age, tumor size and lymph node status before primary treatment were consistent. In 1999, 10-year follow-up data became available for one RCT, and no significant differences in overall survival were found. Two RCTs compared follow-up performed by a hospital-based specialist versus follow-up performed by general practitioners and showed the following results according to outcome:

- Overall survival: no difference between the strategies (HR 1.07; 95% CI 0.64 to 1.78; one RCT; 968 participants; moderate-quality evidence);
- Time elapsed until detection of recurrence: no difference between the strategies (HR 1.06; 95% CI 0.76 to 1.47; two studies; 1,264 participants; moderate-quality evidence);
- Quality of life: no difference between the strategies (one RCT; 356 participants; high-quality evidence);
- Patient satisfaction: greater among patients treated by general practitioners.

One RCT (196 women) compared regularly scheduled follow-up visits versus less frequent visits restricted to the time of mammography. No significant differences emerged in relation to interim use of telephone contacts and frequency of consultations with general practitioners. The authors concluded that follow-up programs based on regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on

regularly performing laboratory and instrumental tests, in terms of the time that elapsed until detection of recurrence, overall survival and quality of life. In two RCTs, follow-up care provided by trained and untrained general practitioners working in an organized practice setting had comparable effectiveness to that delivered by hospital-based specialists, in terms of overall survival, detection of recurrence and quality of life. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001768.pub3/full.

Regular self-examination or clinical examination for early detection of breast cancer

The practice of clinical breast examination and breast self-examination has been widely disseminated and advocated for years as a general screening method for diagnosing breast cancer. This systematic review[14] aimed to assess the clinical effectiveness of these practices and found two large population-based studies (n = 388,535 women) that had been conducted in Shanghai and Russia, comparing breast self-examination with no intervention (control group). The results showed:

- There was no statistically significant difference in breast cancer mortality between the groups (RR 1.05; 95% CI 0.90 to 1.24; 587 deaths in total);
- In Russia, more cancers were diagnosed in the self-examination group than in the control group (RR 1.24; 95% CI 1.09 to 1.41), whereas in Shanghai there was no statistical difference between the groups (RR 0.97; 95% CI 0.88 to 1.06);
- In the screening groups, nearly twice as many biopsies (n = 3,406) with benign results were conducted, compared with the control group (n = 1,856) (RR 1.88; 95% CI 1.77 to 1.99).

Another large population-based study on combined breast self-examination and clinical breast examination was also included, but this study was discontinued due to lack of compliance with follow-up, and no conclusions were drawn. The authors of the systematic review concluded that there was no suggestion of any beneficial effect from breast self-examination screening. Rather, there was only increased harm due to increased numbers of benign lesions identified, with consequently increased numbers of biopsies performed. Therefore, screening by means of physical examination and breast self-examination is no longer recommended. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003373/full.

Screening for breast cancer via mammography

This review[15] aimed to assess the benefits and harm of mammographic screening for breast cancer. It included seven RCTs (600,000 women, of ages ranging from 39 to 74 years) in which results from mammographic screening and without mammographic screening were compared. The pooled results from three RCTs with good methodological quality showed that mammographic screening did not reduce:

- Breast cancer-related mortality after 13 years (RR 0.90; 95% CI 0.79 to 1.02);
- All cancer-related mortality, including breast cancer, after 10 years (RR 1.02; 95% CI 0.95 to 1.10);
- All-cause mortality after 13 years (RR 0.99; 95% CI 0.95 to 1.03).

The total numbers of lumpectomies and mastectomies were significantly larger (31% higher) in the screened groups (RR 1.31; 95% CI 1.22 to 1.42), as were the numbers of mastectomies (20% higher) (RR 1.20; 95% CI 1.08 to 1.32). The use of chemotherapy and radiotherapy was similarly increased in both groups (screened and non-screened). The authors concluded that if the overdiagnosis and overtreatment rates were 30%, 10 years of screening on 2000 women would have the outcomes that one women would avoid dying of breast cancer and 10 healthy women would be treated unnecessarily. Also, 200 women would experience significant psychological distress (anxiety and uncertainty) due to false-positive findings. Furthermore, the authors stated that given the substantial advances in treatment and the greater breast cancer awareness that had been achieved since the time when these RCTs were undertaken, it was most likely that the absolute effect of screening at the time of writing was smaller than at the time of the trials. They also noted that there were recent studies showing greater degrees of overdiagnosis and very little or no reduction in the incidence of advanced cancers through screening. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001877.pub5/full.

Screening for colorectal cancer using the fecal occult blood test (Hemoccult)

The fecal occult blood test (FOBT) is used as a population-based screening for reducing mortality due to colorectal cancer. This review[16] evaluated whether screening using FOBT (guaiac or immunochemical) indeed reduces colorectal cancer mortality and what the benefits and harm from screening might be. Meta-analyses on four RCTs showed that participants allocated to FOBT screening had a reduction in the risk of colorectal cancer mortality of 16%, compared with no FOBT screening (RR 0.84; 95% CI 0.78-0.90). The authors concluded that benefits from the screening included: moderate reduction in mortality due to colorectal cancer; possible reduction in the incidence of cancer through detection and removal of colorectal adenomas; and, potentially, the less invasive surgery that earlier treatment of colorectal cancers may involve. The harmful effects from the screening included: the psychosocial consequences of receiving a false-positive result; the potentially significant complications of

colonoscopy or a false-negative result; the possibility of overdiagnosis (leading to unnecessary investigations or treatment); and the complications associated with treatment. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001216.pub2/full.

Flexible sigmoidoscopy versus fecal occult blood testing for colorectal cancer screening

Screening using FOBT and flexible sigmoidoscopy have been shown to reduce mortality due to colorectal cancer in randomized controlled trials. The objective of this review[17] was to compare the effectiveness of screening for colorectal cancer using flexible sigmoidoscopy versus screening using the FOBT. For this purpose, a search for RCTs comparing screening using flexible sigmoidoscopy or FOBT, with each other or with no screening, was conducted. Only studies reporting mortality due to colorectal cancer were included. FOBT had to be repeated (annually or biennially).

Nine RCTs involving 338,467 individuals randomized to screening and 405,919 individuals to control groups were identified. Five RCTs compared flexible sigmoidoscopy with no screening and four studies compared repetitive guaiac-based FOBT (annually and biennially) with no screening. No studies directly comparing the two screening methods were found. Colorectal cancer mortality was lower when flexible sigmoidoscopy was used (RR 0.72; 95% CI 0.65 to 0.79; high-quality evidence) than with no screening and when FOBT was used (RR 0.86; 95% CI 0.80 to 0.92; high-quality evidence). Based on indirect comparison of the two screening methods, the RR of dying due to colorectal cancer was 0.85 (95% CI 0.72 to 1.01; low-quality evidence) for screening using flexible sigmoidoscopy, in comparison with FOBT. No complications occurred after the FOBT test itself, but 0.03% of the participants suffered a major complication after follow-up. Among more than 60,000 flexible sigmoidoscopy screening procedures and almost 6,000 work-up colonoscopies, a major complication was recorded in 0.08% of the participants. The authors concluded there was high-quality evidence showing that screening by means of flexible sigmoidoscopy and FOBT reduced the mortality due to colorectal cancer. On the other hand, there was low-quality indirect evidence that screening using one of the approaches reduced colorectal cancer deaths more than the other. Major complications associated with screening require validation from studies with more complete reporting of harm. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009259.pub2/full.

Alpha-fetoprotein and/or ultrasonography for liver cancer screening in patients with hepatitis B

This review[18] included three RCTs, and each of them used a different method for liver cancer screening. The first one, conducted in Shanghai, China, randomized the participants to screening every six months using alpha-fetoprotein and ultrasonography (n = 9,373) versus no screening (n = 9,443). The second trial, conducted in Toronto, Canada, on 1,069 participants with chronic hepatitis B, compared screening every six months with alpha-fetoprotein alone (n = 532) versus alpha-fetoprotein and ultrasound (n = 538) over a five-year period. The last study, conducted in Taiwan, was designed as a cluster randomized trial to determine the optimal interval for screening using alpha-fetoprotein and ultrasound. Screening intervals of 4 and 12 months were compared in the groups.

The results from the first two studies did not show any significant conclusions. The third study only showed increased incidence of hepatocellular carcinoma in the four-monthly screening group.

None of the three trials included any reports on adverse events. The authors of this systematic review judged that the specificity and sensitivity of the trials were poor.

The results were inconclusive since there was not enough evidence to evaluate the value of alpha-fetoprotein or ultrasound screening, or both, for patients with hepatocellular carcinoma who were positive for hepatitis B surface antigen (HBsAg). For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002799.pub2/full.

Screening for lung cancer

The objective of this review[19] was to determine whether screening for lung cancer (using sputum examinations, chest radiography or chest computed tomography) reduced mortality. Eight RCTs and one non-randomized trial (453,965 subjects) were included and these showed the following:

- Comparison of annual chest X-ray screening for smokers and non-smokers versus no screening: no reduction in lung cancer mortality (RR 0.99; 95% CI 0.91 to 1.07; one study);
- Comparison of different frequencies of chest X-ray screening: frequent screening was associated with an 11% relative increase in mortality due to lung cancer, compared with less frequent screening (RR 1.11; 95% CI 1.00 to 123; low-quality evidence);
- Comparison of screening using chest X-ray plus sputum cytological tests versus screening using chest X-ray alone: no reduction in lung cancer mortality (RR 0.88; 95% CI 0.74 to 1.03);
- Comparison of annual low-dose computed tomography screening versus annual chest X-ray screening for high-risk smokers and ex-smokers: low-dose computed tomography screening was associated with a 20% decrease in mortality due to lung cancer (RR 0.80; 95% CI 0.70 to 0.92).

The authors concluded there was no current evidence to support screening for lung cancer using chest radiography or sputum

cytological tests. Annual low-dose computed tomography screening was correlated with a reduction in lung cancer mortality among high-risk smokers. However, it is essential to obtain further data on the cost-effectiveness of screening and the relative harm and benefits of screening across a range of different groups at risk and different settings. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001991.pub3/full.

Screening programs in oral cancer

This review[22] aimed to assess the effectiveness of screening (using visual examination, toluidine blue, fluorescence imaging or brush biopsy) for early detection and prevention of oral cancer. Only one RCT, with a 15-year follow-up, met the inclusion criteria. This RCT found that there was a 24% reduction in mortality associated with screening (30/100,000 person-years versus 39/100,000; RR 0.76; 95% CI 0.60 to 0.97) among high-risk individuals who used tobacco or alcohol or both. Moreover, the screening group presented a 19% reduction in the number of individuals diagnosed with oral cancer in stage 3 or higher (RR 0.81; 95% CI 0.70 to 0.93). The authors concluded that there was evidence that visual examination as part of a population-based screening program could reduce oral cancer mortality among high-risk individuals and that there was a reduction in staging and an improvement in survival across the population. There was no evidence to support use of adjunctive technologies (including toluidine blue, brush biopsy or fluorescence imaging) as a screening tool to reduce oral cancer mortality. However, the evidence was limited to one study that presented high risk of bias and which did not consider the effect of cluster randomization in the analysis. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004150.pub4/full.

Screening for prostate cancer

Routine mass, selective or opportunistic screening for prostate cancer has resulted in considerable debate regarding whether this screening indeed reduces mortality and improves quality of life. The objectives of this systematic review[23] were to assess whether screening for prostate cancer reduces prostate cancer-specific mortality or all-cause mortality and to determine its impact on quality of life and adverse events, so as to better inform decision-making relating both to individual patients and to healthcare policy.

Five RCTs (341,342 participants, aged from 45 to 80 years, with duration of follow-up from 7 to 20 years) were included and all of them involved prostate-specific antigen testing, with or without digital rectal examination. There was no significant difference in prostate cancer-specific mortality between the screened and non-screened groups (RR 1.00; 95% CI 0.86 to 1.17). Three RCTs presented high risk of bias, and the other two were classified as having low risk of bias, but provided contradictory results, as follows:

- The European Randomized Study of Screening for Prostate Cancer (ERSPC) reported that screening led to a significant reduction in prostate cancer-specific mortality (RR 0.84; 95% CI 0.73 to 0.95). This study was the only RCT that reported a significant reduction in prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years of age.
- The US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported that screening did not lead to any significant benefit (RR 1.15; 95% CI 0.86 to 1.54).

A meta-analysis on these two studies with low risk of bias alone (ERSPC and PLCO) showed that there was no significant difference in prostate cancer-specific mortality (RR 0.96; 95% CI 0.70 to 1.30). Prostate cancer was diagnosed significantly more frequently among screened men than among unscreened men (RR 1.30; 95% CI 1.02 to 1.65). Localized prostate cancer was diagnosed more frequently among screened men (RR 1.79; 95% CI 1.19 to 2.70), and advanced prostate cancer was diagnosed less frequently among screened men (RR 0.80; 95% CI 0.73 to 0.87).

Screening led to a variety of harms, including bleeding, bruising, short-term anxiety, overdiagnosis and overtreatment, infection, blood loss, requirement of transfusion, pneumonia, erectile dysfunction and incontinence. The adverse events related to biopsies guided by transrectal ultrasound (TRUS) included infection, bleeding and pain. No deaths were directly related to any biopsy procedure. None of the RCTs provided any detail about quality of life as an outcome. The authors concluded that prostate cancer screening did not significantly decrease prostate cancer-specific mortality. A single RCT (ERSPC) found a 21% reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years. A meta-analysis showed that there was no significant reduction in prostate cancer-specific or overall mortality. Harm of moderate severity is frequently associated with prostate cancer-specific screening and further diagnostic evaluations. Overdiagnosis and overtreatment occur frequently and are associated with treatment-related harm. Individuals need to be aware of this when they are deciding whether to undergo screening. A reduction in prostate cancer-specific mortality may take up to 10 years to accrue and therefore men whose life expectancy is less than 10 to 15 years need to be aware that screening is unlikely to be beneficial. No studies examined the independent role of screening by means of digital rectal examination. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004720.pub3/full.

Six systematic reviews that did not find any primary study that fulfilled their inclusion criteria (empty reviews) were also included in our review. Their aims were to evaluate the following:

- Screening using urinary dipsticks for reducing morbidity and mortality;[11]
- Mammography versus mammography plus ultrasonography for breast cancer screening testing in women at average risk;[13]
- Screening for nasopharyngeal cancer;[20]
- Screening for esophageal cancer;[21]
- Screening for testicular cancer;[24]
- Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test.[25]

Thus, no recommendations in relation to the topics of these six systematic reviews can be made until primary studies, preferably RCTs with strong methodological quality, have been published.

DISCUSSION

The present study included 17 Cochrane systematic reviews: 15 relating to screening for specific types of cancer and 2 to screening for cancer in general. However, 6 of the 17 reviews did not find any clinical trial that met the inclusion criteria, and therefore the authors of those "empty reviews" were unable to provide recommendations on the benefits and risks of screening. These last reviews were on screening for bladder, breast, nasopharyngeal, esophageal, testicular and cervical cancer.

Many clinical trials included in the systematic reviews were small, had short-term follow-up and were of poor methodological quality, which limited the quality of evidence available for many relevant outcomes. This was notable in relation to the reviews on screening among individuals with idiopathic deep venous thrombosis,[10] screening for hepatocellular carcinoma among individuals with chronic hepatitis B[18] and screening for oral cancer in the general population.[22]

Regarding the screening strategies most commonly used by professionals on populations, a systematic review[14] showed that routinely performed breast self-examination did not reduce cancer mortality and also doubled the number of biopsies with benign outcomes.

There continues to be discussion concerning mammography for breast cancer screening. On the basis of a Cochrane systematic review, mammographic screening does not seem to have benefits regarding breast cancer mortality or cancer-related mortality after 10 and 13 years respectively.[15]

For prostate-specific antigen testing with or without digital rectal examination for prostate cancer screening, the results from the two major RCTs are inconsistent regarding the benefits relating to mortality.[23]

Regarding the implications of this study for clinical practice, the evidence found here does not support most routinely performed screening approaches, given their lack of clinical effectiveness. Patients need to be aware of the risks of false-positive and false-negative results before undergoing screening tests.

Concerning the implications of this study for further research, since only four systematic reviews provided high-quality bodies of evidence, there is a clear need for better designed and better conducted clinical trials for assessing the clinical outcomes of the various screening methods that are frequently used in clinical practice and for assessing the effectiveness of screening for the vast majority of cancers.

CONCLUSION

This overview brought together 17 systematic reviews with distinct variations in the level of evidence presented, from low to high. The evidence found in this overview did not support most of the commonly used screening tests for cancer. Therefore, we take the view that patients need to be aware of, and well-informed about the possibilities of false positives and false negatives before undergoing such tests. The number of studies with high-quality evidence level pointing towards significantly decreased mortality was low. These studies addressed two issues: low-dose computed tomography for high-risk individuals, which seemed to reduce lung cancer mortality; and flexible sigmoidoscopy and fecal occult blood tests, which seemed to reduce colorectal cancer mortality.

Further studies with better quality are needed in order to assess the effectiveness of screening tests for cancer as well their side effects.

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9. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). The author should also indicate a postal address, e-mail address and telephone number that can be published together with the article.

Main document

Second page: abstract and keywords

The second page must include the title and a 250-word abstract in English (case reports with 100 words). Do not cite references in the abstract.

Use the following headings:

1. Background: Describe the rationale for the study including the research question or the scientific hypothesis.
2. Design and setting: Declare study design correctly,[11] and the setting.
3. Methods: Describe methods briefly.
4. Results: Describe primary results with quantitative results describing the sampling strategy.
5. Conclusions: Make a succinct statement of data interpretation answering the research question presented previously.
6. Clinical Trial Registration. Mandatory for clinical trials, optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.

Insert 3 to 5 key words after the abstract, with terms differing from the title. The words must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.

Text

- Typical main headings include Introduction, Methods, Results, Discussion and Conclusion. The authors can use short subheadings too.
- Number the pages.

- Abbreviations must be avoided.
- A maximum of 3000 words in the main text, from the Introduction to the Conclusions; 1000 words for short communications.
- Maximum number of figures and/or tables is 5
- Maximum number of references is 35 (except for systematic reviews).

References

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

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

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent a resolution of 300 DPI and/or minimum size of 2500 pixels (width) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint or Microsoft Word documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Graphs prepared in Microsoft Excel (do not send them in image formats) spreadsheets must be accompanied by the tables of data from which they have been generated.

All the figures and tables should be cited in the text.

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded to indicate the magnification used. The staining agent should be specified in the figure legend.

Original articles

Clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis, are considered to be full-text original articles, with a maximum of 3000 words.

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles.

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion). The abstracts in short communications should not be structured and have a maximum of 100 words.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement[5,6]
2. Clinical trials: CONSORT Statement[2]
3. Accuracy studies on diagnostic tests: STARD Statement[8,9]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]
5. Case reports: CARE[7]

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials have only been accepted for publication if they have received an identification number from one of the clinical trial registers (the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Short communications, case reports, case series and narrative reviews

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion), a maximum of five references and one figure or table. They should be structured in the same way as original articles. Individual case reports should contain the following sections: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

Both short communications and case reports must be submitted with abstracts and keywords. The abstracts in short communications should not be structured and have a maximum of 100 words.

The São Paulo Medical Journal is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[11] The search strategy for each database and the number of articles obtained from each database must be shown in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms are appropriate to be utilized for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT) the search dates should be indicated in the text or in the table.

Narrative reviews may be accepted by the São Paulo Medical Journal provided that a systematic search is made, and they should be structured as Original Articles. The search strategy and results should be presented as described above for case reports. By invitation from the Editor-in-Chief, narrative reviews addressing historical personal or collective experiences relating to clinical health sciences, epidemiology and public health may be accepted, but with no more than two authors.

Individual case reports should contain Introduction, Case Report, Discussion and Conclusion. Case reports should be structured in accordance with the norms of the CARE Statements.[7] Case reports published in São Paulo Medical Journal must be submitted with abstracts and keywords.

Letters to the editor

Letters to the editor may address articles published in the São Paulo Medical Journal publication or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

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