ISSN 1516-3180

São Paulo Medical Journal/Evidence for Health Care, 2016 April 7; 134(2):95-184

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

Medline, Lilacs, SciELO, Science Citation Index Expanded, Journal Citation Reports/ Sciences Edition (impact factor 0.723) and EBSCO Publishing

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ORGANIZATION

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

Editors: Paulo Andrade Lotufo and Álvaro Nagib Atallah.
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Desktop publishing: Zeppelini Editorial (www.zeppelini.com.br).
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• One-year subscription for the year 2016: individual US$ 165; institutional US$ 230.

Scientific Council

Diretoria Executiva da Associação Paulista de Medicina (Triênio 2014-2017)

Zika epidemic and social inequalities: Brazil and its fate

Epidemia de zika e desigualdades sociais: Brasil e seu destino

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In January 2001, I wrote an editorial on this page with the title "Coffee, Samba, Football, AIDS and Social Inequality in Brazil." The first paragraph described a contradiction within the Brazilian National Health System: "The most important newspapers and magazines worldwide (The New York Times, Le Monde, The Wall Street Journal, Time Magazine) have been publishing the tremendous results from the Brazilian AIDS program. This is a combination of preventive measures and free distribution of antiretroviral drugs with an impressive fall in hospitalizations and mortality. Now, the Brazilian program has become the paramount public health effort for halting the AIDS epidemic to be followed in other places, especially the sub-Saharan African countries. In contrast, the Health Department of São Paulo State is warning about increasing case-fatality rates of tuberculosis. How can this contradiction be explained for a non-Brazilian?"[1]

Imagine if I published the same editorial again, just changing the phrase "about increasing case-fatality rates of tuberculosis" by "the recent incidence of Zika virus infection and new cases of microcephaly". Readers might think that they could detect an instance of self-plagiarism. Unfortunately, this is not a lazy way to write a comment by copying an older one. The fact is that the players can change, but the play is the same on the stage of Brazilian public health.

The question transcribed above was answered in that editorial in 2001: "for us, Brazilian physicians and medical researchers, the answer is very easy. AIDS is a disease that has afflicted people with real prestige in Brazilian circles of power. In summary: journalists, popular music stars, soap-opera actors and actresses, physicians, scientists, military officers, priests and other well-born citizens who traveled to the USA during the early 1980s and were infected by sexual intercourse in New York City and San Francisco. After that, they spread the virus and disease among Brazilians who had never dreamed of going up the steps on an airplane. Until the early 1990s, in São Paulo City, the incidence of AIDS cases continued to be greater among affluent people than among poor ones. As the spread of AIDS became a menace to the abovementioned professions, it was easy to pressure the Ministry of Health, State Departments of Health, and other authorities to increase the budget for AIDS control and treatment, including sometimes a shift of resources from other programs".[1]

For more than a decade, the Brazilian AIDS program was self-proclaimed as "an example for the world". In contrast, the control over dengue has deteriorated year by year. Despite the manifest failure of control over the dengue epidemic, which has been conceded by most of the communicable disease epidemiologists in Brazil, in an article in *The Lancet*, the federal budget for AIDS has been increasing and the budget for controlling vectors like *Aedes aegypti* is still declining.[2]

THE CASE OF PRE-EXPOSURE PROPHYLAXIS FOR HIV CONTROL

One year ago, the voracious appetite for more money propelled the Brazilian authorities, physicians and AIDS activists to stay on the front-line of the fight against AIDS by advocating adoption by the Brazilian National Health System of a strategy called "pre-exposure prophylaxis" for HIV control. This is a very controversial proposal that will cost $ 13,000/year/per capita. I was invited to wrote an op-ed article in the most-read Brazilian newspaper[3] rebutting the proposal made in the same issue by Luiz Loures, the Deputy Executive Director of UNAIDS (the United

Nations program for combating AIDS), who stated that "PreP should be the opportunity to finish up the AIDS epidemic." (sic)[4]

The basis of my reasoning was that scientific articles supporting the use of pre-exposure prophylaxis presented several limitations, not only from a strictly scientific view, but also from a strategic point of view. In my view, this proposal was a step backwards in relation to preventive efforts towards halting both AIDS and also other sexually transmitted diseases.

THE MEDICAL-INDUSTRIAL COMPLEX

My reasoning in that article in *Folha de S.Paulo* was to refer to Arnold Relman (former editor of the *New England Journal of Medicine*), who wrote a seminal editorial about the concept of the medical-industrial complex. He described this situation as similar to the one of the "military-industrial complex" that Dwight Eisenhower described during his US Presidential term in the 1950s.

In fact, we are under heavy pressure from the "medical-industrial complex," now using UNAIDS as its spokesperson, to take money from other activities such as vector control, in order to put it into the pockets of the AIDS medical industrial complex. What is incredible in this story is that the proposal for pre-exposure prophylaxis relates only to one medicine: Truvada, manufactured by Gilead, in California. The leftist watchdogs who start barking if there is even a one-day delay in free distribution of any HIV medication did not even whimper about any conflict of interest in this case.

One year after this debate, the same newspaper, Folha de S. Paulo published an article signed by the "Vice Brazil Organization" regretting that the Brazilian National Health System still did not include pre-exposure prophylaxis as free medicine. Furthermore, the author stimulated readers to start lawsuits against the Brazilian National Health System to get free drugs so that people could indulge in unsafe sexual intercourse.[5]

THE SAME PLAYERS ON THE STAGE

At the same time that pre-exposure prophylaxis was becoming a motive for great concern within the media located in São Paulo and Rio de Janeiro, less fortunate people in the poorest areas of the country were suffering from dengue, chikungunya and Zika. To the best of my knowledge, no one involved in AIDS activism is either creating some networks for supporting parents and children afflicted by the consequences of Zika infection, or is demanding more funds for combating zika infection.

An editorial by Richard Horton in The Lancet took the view that the Zika epidemic is an opportunity for Brazil to change its public health system.[6] I am skeptical. The reason why the Zika epidemic exists is that the dengue epidemic was neglected because it was limited to poor people, just like tuberculosis was neglected 20 years ago. The President of Brazil, Ms. Dilma Roussef, is mobilizing her staff to halt the *Aedes aegypti* outbreak using military metaphors. She blamed her predecessors, despite the fact that this is her second term. It would be better for us if the President, the Brazilian Congress, the Ministry of Health, the media, the medical establishment and leftist activists could only acknowledge that we have been doing things wrongly for a long time now. Zika is only the play of the season of social inequalities in Brazil.

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Sources of funding: None
Conflict of interests: None

Date of first submission: February 15, 2016
Last received: February 15, 2016
Accepted: February 15, 2016

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DOI: 10.1590/1516-3180.2014.8581009

Determination of a cutoff value for pelvic floor distensibility using the Epi-no balloon to predict perineal integrity in vaginal delivery: ROC curve analysis. Prospective observational single cohort study

Determinação de um valor de ponto de corte para a extensibilidade do assoalho pélvico pelo balão Epi-no para predizer integridade perineal no parto vaginal: análise pela curva ROC. Estudo prospectivo observacional de coorte única

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KEY WORDS:
Physical therapy modalities.
Pelvic floor.
Perineum.
Labor stage, first.
Parturition.

PALAVRAS-CHAVE:
Modalidades de fisioterapia.
Diafragma da pelve.
Períneo.
Primeira fase do trabalho de parto.
Parto.

ABSTRACT

CONTEXT AND OBJECTIVE: Several risk factors are involved in perineal lacerations during vaginal delivery. However, little is known about the influence of perineal distensibility as a protective factor. The aim here was to determine a cutoff value for pelvic floor distensibility measured using the Epi-no balloon, which could be used as a predictive factor for perineal integrity in vaginal delivery.

DESIGN AND SETTING: Prospective observational single cohort study conducted in a maternity hospital.

METHODS: A convenience sample of 227 consecutive at-term parturients was used. All women had a single fetus in the vertex presentation, with up to 9.0 cm of dilation. The maximum dilation of the Epi-no balloon was measured using a tape measure after it had been inflated inside the vagina up to the parturients' maximum tolerance. The receiver operating characteristic (ROC) curve was used to obtain the Epi-no circumference measurement with best sensitivity and specificity.

RESULTS: Among the 161 patients who were included in the study, 50.9% underwent episiotomy, 21.8% presented lacerations and 27.3% retained an intact perineum. Age > 25.9 years; number of pregnancies > 3.4; number of deliveries > 2.2 and circumference measured by Epi-no > 21.4 cm were all directly correlated with an intact perineum. Circumference measurements using the Epi-no balloon that were greater than 20.8 cm showed sensitivity and specificity of 70.5% and 66.7% (area under curve = 0.713), respectively, as a predictive factor for an intact perineum in vaginal delivery.

CONCLUSION: Circumferences greater than 20.8 cm achieved using the Epi-no balloon are a predictive factor for perineal integrity in parturients.

RESUMO

CONTEXTO E OBJETIVO: Diversos fatores de risco estão envolvidos nas lacerações do períneo durante o parto vaginal, contudo, pouco se sabe sobre a influência da extensibilidade perineal como um fator protetor. O objetivo foi avaliar o ponto de corte da extensibilidade do assoalho pélvico medido pelo balão Epi-no, o qual poderia ser usado como fator preditor de integridade perineal no parto vaginal.

TIPO DE ESTUDO E LOCAL: Estudo prospectivo observacional de coorte única conduzido em maternidade.

MÉTODOS: Uma amostra de conveniência de 277 parturientes consecutivas no termo foi utilizada. Todas as mulheres tinham feto único com apresentação cefálica fletida, com até 9,0 cm de dilatação. A máxima dilatação do balão Epi-no foi medida com fita métrica após a sua insuflação dentro da vagina até a tolerância máxima da parturiente. Uma curva característica de operação do receptor (ROC) foi utilizada para obter a medida da circunferência com a melhor sensibilidade e especificidade.

RESULTADOS: Dentre as 161 pacientes que foram incluídas no estudo, 50,9% sofreram episiotomia, 21,8% lacerações e 27,3% tiveram o períneo intacto. Idade > 25,9 anos; número de gestações > 3,4; número de partos > 2,2; e medida do perímetro do Epi-no > 21,4 cm foram todos diretamente correlacionados com períneo intacto. Os valores do perímetro com o balão Epi-no que estavam acima de 20,8 cm mostraram sensibilidade e especificidade de 70,5% e 66,7% (área sob a curva = 0,713), respectivamente, como fator preditor de períneo intacto no parto vaginal.

CONCLUSÃO: Circunferência medida pelo balão Epi-no maior que 20,8 cm é fator preditor de integridade perineal em parturientes.

INTRODUCTION

The pelvic floor muscles are a complex involving two layers of muscles. One layer involving the levator ani and puborectalis muscles is deeper and the other is more superficial and involves the perineum.[1]

Vaginal delivery has been considered to be an important predictive factor for pelvic floor dysfunction, including urinary or fecal incontinence, genital prolapse and levator trauma.[2] This is due to the extensive stretching of the pelvic floor during delivery. Cesarean section reduces the risk of pelvic floor trauma but is not entirely protective.[3]

It has been proven that vaginal delivery increases the levator hiatal dimensions, especially after an avulsion injury.[4] In a prospective cohort study on 39 women who delivered vaginally, three-dimensional translabial ultrasound was performed during the postpartum period and was repeated two and six months after delivery. Levator avulsion occurred in 39%, and vaginal delivery was correlated with higher maternal age, operative delivery and worsened stress incontinence postpartum.[5] In another study, levator hiatal area > 25 cm in the Valsalva maneuver, measured by three-dimensional ultrasound, was defined as abnormal distensibility or "ballooning" of the levator hiatus.[6]

The most severe obstetric perineal lesions occur when the soft tissue, muscle, fascia, adipose tissue, skin and mucosa are not sufficiently extensible to permit fetal passage. However, these soft perineal tissues can distend, and the extent of the distension varies both between parturients and between pregnancies within an individual. Moreover, this distension can be reduced or increased during the course of the pregnancy by promoting shrinkage or stretching of the soft perineal tissues, respectively, using physiotherapeutic methods.[7]

Some risk factors for perineal trauma during vaginal delivery have already been established, and these include advanced maternal age, "Caucasian and Asian" races, high maternal body mass index, operative vaginal deliveries, a prolonged expulsive period and high birth weight of the newborn.[8-10] However, there is a lack of studies on the importance of pelvic floor distensibility and its relationship with birth trauma. Distensibility of the perineum is very important during the second stage of labor, for preventing birth trauma, because of the high pressure imposed by the fetus head on the muscles of the pelvic floor.[11]

The Epi-no Delphine Plusvaginal dilator (Starnberg Medical, Tecsana GmbH, Munich, Germany) consists of an inflatable silicone balloon connected to a manometer via a rubber tube.[12] Recently, Kubotani et al.[13] compared perineal distensibility using Epi-no in 23 singleton and 20 twin pregnancies. There was no difference in perineal distensibility between the two groups, but there was a positive correlation between perineal distensibility and abdominal circumference in twin pregnancies.

OBJECTIVE

Because of the absence of an instrument for objectively and quantitatively assessing the maximum degree of pelvic floor distensibility, we decided to use the Epi-no device as a method for measuring this biomechanical property. Thus, the aim of this study was to determine a cutoff value, in centimeters, for pelvic floor distensibility measured using the Epi-no balloon, which could be used as a predictive factor for muscle integrity in vaginal delivery.

METHODS

A prospective observational single cohort study was conducted at the Amador Aguiar Maternity Hospital (HMMAA), in Osasco, state of São Paulo, Brazil, between January and December 2009. The project was evaluated and approved by the Research Ethics Committee of Universidade Federal de São Paulo (Unifesp), under registration number 1283/08, and by the National Research Ethics Committee, under report number 676. HMMAA is the largest public maternity hospital in Osasco and provides care for low-risk pregnancies (70%) and high-risk pregnancies (30%), at a rate of 600 deliveries/month.

The study included 227 consecutive at-term single births in the cephalic presentation with up to 9.0 centimeters of dilatation and at a maximum station of zero, based on the American College of Obstetrics and Gynecologists classification of fetal head station assessments.[14] We included both primiparous and multiparous parturients. Only collaborative parturients who wished to undergo the examination, who had not received anesthesia (e.g. rachidian, peridural or combined block) and whose fetus showed good vitality at the time of the assessment were included.

Patients firstly read and signed the informed consent form. If the patient was still a teenager, her mother needed to provide consent and sign for her. The participants then underwent pelvic floor distensibility assessment (comprising pelvic floor and perineum), which was measured as the circumference in centimeters of the inflated balloon of the Epi-no device (Starnberg Medical, Tecsana GmbH, Munich, Germany). This was done upon admission to the delivery room. The Epi-no circumference measurements were made by a single examiner (MRDZ), who had had four years of experience of using the Epi-no balloon for perineal muscle training during pregnancy. To reduce the bias of individual tolerance, all parturients received information regarding the safety of this device through the assurance that its use does not increase the risk of vaginal infection.[15]

For the test, the parturients were placed in the dorsal decubitus position with flexed and abducted lower limbs (from 30° to 45°) and with their feet supported on the bed. They were asked not to contract their gluteal, perineal or adductor muscles. The balloon was covered with a condom and, after application of a gel lubricant, was introduced into the vagina until only two centimeters were

visible outside the vaginal introitus. This was the assurance that the balloon had reached not only the superficial layer of the pelvic floor (perineum) but also the deepest layer (including the levator ani muscle). The balloon was then gradually inflated until the tolerable limit, which was subjectively determined by the patient, was reached. All of the patient assessments were performed by the same examiner. Next, the balloon was slowly withdrawn while still fully inflated, the condom was removed and the largest circumference of the balloon was measured using a measuring tape.

The sample size was estimated such that sufficient precision would be attained, i.e. a 95% confidence interval (CI) of width = 0.20, if the observed area under receiver operating characteristic (ROC) curve was greater than 0.60.[16] For an the area under the ROC curve of 0.713, we would need to assess 160 subjects to have a 95% CI width ≤ 0.20.

The perineal trauma was classified based on third-degree laceration (when the extent of the lesion included the external anal sphincter totally or partially) and fourth-degree laceration (when the rectal mucosa was involved).[17] The diagnosis of perineal trauma was made both by doctors and by the midwifes who assisted the labor, but the repairs were made only by doctors.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v.14 (SPSS Inc., Chicago, IL, USA) and Minitab v.13 (Minitab Inc., State College, PA, USA). The sample size used for our study provided a power of 82.7%. First of all, descriptive statistics were produced on all the variables studied (age, number of gestations and deliveries, body mass index, pelvic floor muscle extensibility, newborn weight and newborn cephalic circumference). Next, univariate analysis was applied to determine which variables influenced perineal outcomes. Student's t test for analysis of continuous variables and the Mann-Whitney test were used when the data were not normally distributed. After that, multivariate logistic regression was used, taking into consideration all the significant variables of the univariate analysis at a significance level of 20%. Adjusted multivariate logistic regression was performed by means of a backward process. Appropriate odds ratios (OR) with 95% CI were calculated. Probability values < 0.05 were regarded as statistically significant.

RESULTS

Initially, we assessed 227 parturients, of whom 117 were nulliparous and 110 were multiparous. White, mixed and black skin color corresponded to 45.8%, 44.9% and 8.8%, respectively. Following delivery, 66 patients (29.1% of the cohort) were excluded from the analysis: 57 (25.1%) because their delivery was via cesarean section, eight (3.5%) because they did not provide sufficient medical data and one (0.44%) because the patient left the hospital against medical advice. There was no use of forceps or vacuum extractor device for assisting in any parturient's delivery.

The patients were not followed up after delivery, because the hospital where this study was conducted is a public hospital that only provides delivery care, while puerperium follow-up is provided at several primary healthcare units in the metropolitan region of São Paulo. Hence, proper follow-up for perineal trauma cases was impossible.

The 161 remaining parturients averaged 23.6 ± 5.1 years of age with an average body mass index of 27.6 ± 4.3 kg/m^2. The patients had an average Epi-no balloon maximum circumference of 19.9 ± 2.7 cm and gave birth to newborns that weighed 3,168 ± 428 g with a head circumference of 34.1 ± 1.5 cm.

With regard to the perineal outcomes of the 161 patients who were included, 50.9% (n = 82 patients) received right mediolateral episiotomy, 21.8% (n = 35) suffered laceration and 27.3% (n = 44) maintained an intact perineum. The perineal outcomes were then analyzed based on variables including age, number of pregnancies, parity, body mass index, Epi-no balloon circumference, newborn weight and newborn head circumference. These parameters are presented in **Table 1**.

Table 1. Univariate analysis from predictive factors for perineal integrity after vaginal delivery

Variable	Perineal outcomes	n	Mean	Standard deviation	P-value
Age (years)	Perineal trauma	117	22.8	5.0	0.001*
	Intact perineum	44	25.9	4.9	
Number of pregnancies	Perineal trauma	117	1.57	0.93	< 0.001†
	Intact perineum	44	3.36	2.25	
Parity	Perineal trauma	117	0.43	0.75	< 0.001†
	Intact perineum	44	2.18	1.95	
Body mass index (kg/m^2)	Perineal trauma	117	27.75	4.27	0.22
	Intact perineum	44	26.86	4.04	
Distensibility (cm)	Perineal trauma	117	19.37	2.81	< 0.001*
	Intact perineum	44	21.36	2.03	
Newborn weight (kg)	Perineal trauma	117	3.18	0.39	0.131
	Intact perineum	44	3.06	0.45	
Newborn head circumference (cm)	Perineal trauma	117	34.17	1.50	0.400
	Intact perineum	44	33.94	1.52	

*Student-t test; †Mann-Whitney test.

The results from adjusted multivariate logistic regression using the backward process are presented in **Table 2**. This shows that greater parity, higher distensibility (Epi-no balloon values) and lower newborn weight were predictive factors for perineal integrity.

The ROC curve was constructed, and this demonstrated that an Epi-no circumference measurement of 20.8 cm was the best cutoff for perineal integrity after vaginal delivery (area under curve = 0.713; sensitivity of 70.5% and specificity of 66.7%) (**Figure 1**).

DISCUSSION

According to Astrand and Rodahl,[18] muscle fibers have biomechanical properties such as excitability, contractility, distensibility and elasticity. Distensibility and elasticity differ because the former property indicates the extent to which a fiber can distend during a stretch stimulus, and the latter indicates how well the fiber can return to its original length following the stretch stimulus.

To the best of our knowledge, no previous study has objectively investigated the maximum distensibility of the pelvic floor muscles. Shek and Dietz[19] studied the influence of levator ani distensibility on occurrences of levator avulsion after vaginal delivery. They concluded that the levator avulsion could not be predicted antenatally, but they measured the pelvic floor distensibility using transperineal ultrasound when the women were doing a Valsalva maneuver. It is possible that, during this maneuver, the levator muscle does not achieve its maximum distensibility, because for this to occur, it would have to be stretched passively, i.e. the muscle would need to be relaxed while a movement elongating it and separating its origin from its insertion was being performed.[20] However, our study did not have the objective of assessing levator avulsion.

Table 2. Final results from multivariate logistic regression using backward process

Variables	Odds ratio	95% confidence interval	P-value
Parity	3.27	2.10-5.10	< 0.001
Perineal distensibility (cm)	1.33	1.11-1.60	0.002
Newborn weight (kg)	0.17	0.05-0.56	0.004

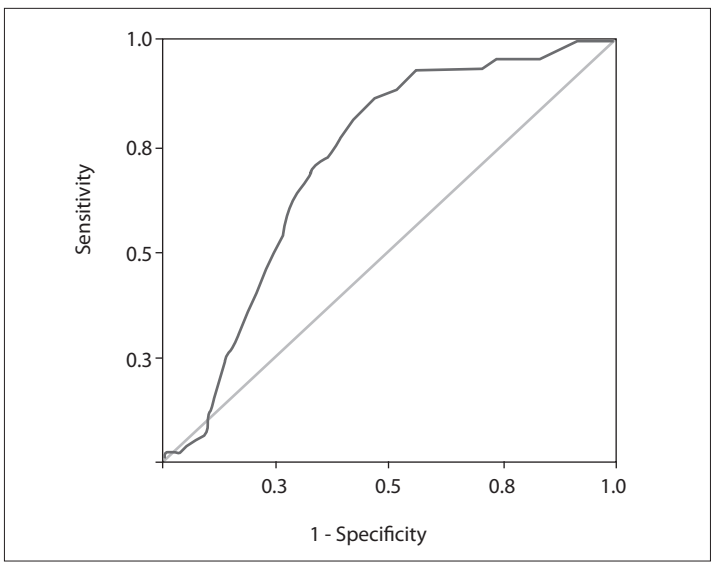

Figure 1. Receiver operating characteristic (ROC) curve for perineal integrity assessment using the *Epi-no* circumference measurement. Area under curve = 0.713; sensitivity of 70.5% and specificity of 66.7%.

In the present study, an inflatable balloon was introduced into the vagina and was inflated to produce substantial distension of the pelvic floor muscles. A measure of muscle distension can then be obtained by measuring the circumference of the fully inflated balloon. Although the device was not originally designed for this purpose, this adaptation was necessary because no alternative method for measuring perineal distensibility is currently available.

One of the most frequent complaints from patients regarding vaginal birth is the fear of a perineal lesion (as occurs with episiotomy or laceration, for example) that could lead to sexual dysfunction after delivery.[21] In some Latin American countries, including Brazil, the incidence of cesarean sections is as high as 80% in private care and leads to persistent concern within the healthcare system.[22] Introduction of a test that could predict the likelihood that a lesion would not occur might allow the expectant mother to be more comfortable and "secure" in opting for vaginal delivery. In this regard, predictive factors for pelvic floor lesions during vaginal birth should be studied further. Although some factors predictive of lesions have been identified, such as a prolonged expulsion period, a macrosomic fetus, advanced maternal age, ethnicity and high body mass index, pelvic floor distensibility has received little attention.

Two previous studies investigated the use of the Epi-no balloon trainer to prepare the perineum for vaginal delivery and to reduce levator trauma. In the first of these, Ruckhäberle et al.[15] conducted a prospective, randomized study using Epi-no during pregnancy for perineal preparation (to increase muscle extensibility) prior to birth. A total of 135 primigravidae participated in the study and used the device for at least 15 minutes per day from the 37th gestational week onwards, for an average of 15 consecutive days; a control group of 135 primigravidae did not undergo any perineal preparation. After training, the study group had a mean circumference of 24.3 ± 4.4 cm and showed a tendency towards increased likelihood of having an intact perineum, in comparison with the control group (P = 0.05).

However, there are some possible caveats to the study by Ruckhäberle et al.[15] First, the women were instructed to perform the stretching exercise with the Epi-no device at home

without any previous supervised training. Because using the Epi-no is not straightforward, this could lead to a bias in its application and in the subsequent results. In addition, the pregnant women themselves were instructed to measure the maximum balloon circumference, which could also introduce a bias in the results. Such considerations might explain the primary difference between our results and theirs, in which they reported larger Epi-no circumference measurements. It is important to note that all of our measurements were conducted by the same examiner (MRDZ), which might have produced more reproducible data.

In the second of these investigations on the Epi-no trainer, Shek et al.[23] conducted a randomized controlled trial to assess if the pelvic trainer could reduce levator trauma. The authors selected 200 nulliparous women with singleton pregnancies, and these patients were divided into intervention and control groups. These patients were examined by means of three-dimensional translabial ultrasound at 35-37 weeks and three months after delivery. The patients in the intervention group were instructed to use the Epi no device from the 37th week onwards. A total of 156 women returned for the follow-up examination, of whom 78 had had vaginal deliveries. The risk of avulsion was halved in the intervention group (6% versus 13%; $P = 0.19$). The analysis on the treatment received revealed that the intervention group presented nonsignificant 42% and 30% reductions in levator avulsion and microtrauma, respectively ($P \geq 0.22$). The authors concluded that the Epi no balloon did not reduce the incidence of levator trauma.

One limitation of the present study is that it was difficult for a single examiner to operate the device without assistance. Thus, two examiners were required (AP and CDP), in which the principal researcher introduced the balloon to the correct depth and held it in place while the second examiner inflated the balloon. In addition, it would be also very important to evaluate the patients after delivery, using three-dimensional ultrasound to investigate occurrences of levator avulsion, as done by Dietz and Shek.[24]

In our study, we observed no bleeding, which is consistent with the report by Ruckhäberle et al.,[15] or any other serious complaint. This suggests that it is safe to use this equipment. One previous study reported on a patient who used the Epi-no device and suffered venous air embolism.[25] In this case, the patient's husband helped her to inflate the device, and after ten minutes of inflation, the patient began to complain of vaginal pain and dizziness, after which the device was immediately removed. Following a convulsive period, she became unresponsive and was taken to the emergency service, where a cesarean section was performed, followed by care in the surgical intensive care unit. After two months, she no longer exhibited any neurological sequelae but was counseled regarding the risk of uterine rupture in future pregnancies. The authors of the report hypothesized that the Epi-no device had had an unobserved leak that led to the severe complications. To avoid this potential complication, in the present study we covered the balloon with a condom, which prevented the entry of air during inflation of the balloon. Moreover, although the device has been described as simple to use, we believe that use by an unsupervised nonprofessional can be harmful. However, new studies about the safety of the Epi-no balloon when it is used by healthcare professionals or people without previous training should be conducted to prove the real degree of safety of the Epi-no device.

From a clinical perspective, when a pregnant woman presents a rigid perineum, she could perform local stretching, for example by means of perineal massage and/or use of an Epi-no device, to achieve adequate perineal distensibility.

Some authors have reported that the levator ani muscle can distend during fetal head descent, during vaginal delivery. Lien et al.[26] performed computer simulations on vaginal childbirth and demonstrated that the pubovisceral portion of the levator ani muscle is subject to a stretch ratio of more than 3:1. Similar results were reported by Hoyter et al.,[27] who used magnetic resonance imaging of a nulligravid pelvic floor to create a simulation model and found that the puborectalis muscle can reach a stretch ratio of 3.5:1 during fetal head descent. Although these studies are important for providing indirect knowledge regarding the mechanism of muscle stretching during a vaginal delivery, such simulations cannot consider the mechanical properties of the pelvic floor with regard to the important biomechanical changes that occur during pregnancy and delivery.[27]

In the present study, we evaluated the pelvic floor during maximum stretching during parturition, at which the biomechanical distensibility was at its maximum level. However, the question still remains as to whether these muscles might suffer a more intrinsic, nonvisible form of perineal lesion such as levator avulsion. Thus, this study presented a new method for assessing distensibility, which will allow future researchers to understand the importance of distensibility in conferring protection to the pelvic floor during childbirth.

We believe that the main bias of our study was the inflation of the Epi-no balloon up to the tolerable limit, which was subjectively determined by the patient. However, all patients received information regarding the safety of the Epi-no balloon before using it.

CONCLUSION

In summary, a circumference achieved by the Epi-no balloon that was larger than 20.8 cm was a predictive factor for perineal integrity in these parturients. New studies with large population samples are necessary to prove our results.

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Sources of funding: None
Conflicts of interest: None

Date of first submission: March 18, 2014
Last received: August 25, 2014
Accepted: September 10, 2014

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DOI: 10.1590/1516-3180.2015.9603001

Evaluation of the impact of collaborative work by teams from the National Medical Residency Committee and the Brazilian Society of Neurosurgery. Retrospective and prospective study

Avaliação do impacto do trabalho conjunto das equipes da Comissão Nacional de Residência Médica e da Sociedade Brasileira de Neurocirurgia. Estudo retrospectivo e prospectivo

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KEY WORDS:
Education, medical.
Internship and residency.
Educational measurement.
Program evaluation.
Neurosurgery.

PALAVRAS-CHAVE:
Educação médica.
Internato e residência.
Avaliação educacional.
Avaliação de programas e projetos de saúde.
Neurocirurgia.

ABSTRACT

CONTEXT AND OBJECTIVE: Training for specialist physicians in Brazil can take place in different ways. Closer liaison between institutions providing this training and assessment and health care services may improve qualifications. This article analyzes the impact of closer links and joint work by teams from the National Medical Residency Committee (Comissão Nacional de Residência Médica, CNRM) and the Brazilian Society of Neurosurgery (Sociedade Brasileira de Neurocirurgia, SBN) towards evaluating these programs.

DESIGN AND SETTING: Retrospective and prospective study, conducted in a public university on a pilot project developed between CNRM and SBN for joint assessment of training programs across Brazil.

METHODS: The literature in the most relevant databases was reviewed. Documents and legislation produced by official government bodies were evaluated. Training locations were visited. Reports produced about residency programs were analyzed.

RESULTS: Only 26% of the programs were immediately approved. The joint assessments found problems relating to teaching and to functioning of clinical service in 35% of the programs. The distribution of programs in this country has a strong relationship with the Human Development Index (HDI) of the regions and is very similar to the distribution of specialists.

CONCLUSION: Closer collaboration between the SBN and CNRM had a positive impact on assessment of neurosurgery medical residency across the country. The low rates of direct approval have produced modifications and improvements to the quality of teaching and care (services). Closer links between the CNRM and other medical specialties have the capability to positively change the structure and function of specialty training in Brazil.

RESUMO

CONTEXTO E OBJETIVO: A formação do médico especialista no Brasil pode ocorrer por diferentes vias. A aproximação das instituições que realizam essas formações e avaliam os médicos e as instituições de saúde pode trazer benefícios na qualificação. Este artigo analisa o impacto dessa aproximação e o trabalho conjunto das equipes da Comissão Nacional de Residência Médica (CNRM) e da Sociedade Brasileira de Neurocirurgia (SBN) na avaliação desses programas.

TIPO DE ESTUDO E LOCAL: Estudo retrospectivo e prospectivo, conduzido em uma universidade pública, sobre projeto piloto elaborado entre CNRM e SBN na avaliação conjunta dos programas de treinamento pelo Brasil.

MÉTODOS: Revisão de literatura nas principais bases de dados, documentos e legislações produzidas por órgãos oficiais governamentais, visitas aos locais de formação e análise dos relatórios e pareces produzidos sobre os programas de residência médica.

RESULTADOS: Apenas 26% dos programas foram aprovados diretamente. As avaliações conjuntas encontraram problemas relacionados ao ensino e ao funcionamento do serviço em cerca de 35% dos programas. A distribuição dos programas no país tem forte relação com o Índice de Desenvolvimento Humano (IDH) das regiões e é muito semelhante à distribuição dos especialistas.

CONCLUSÃO: A aproximação da SBN com a CNRM teve impacto positivo na avaliação das residências médicas em neurocirurgia no país. Os índices baixos de aprovação direta forçaram a realização de modificações e melhorias na qualidade de ensino e assistência (serviço). A aproximação da CNRM e das demais especialidades médicas pode alterar positivamente a estrutura e o funcionamento da formação médica no país.

INTRODUCTION

The world is currently facing a lack and poor distribution of healthcare professionals.[1] Many institutions and official bodies around the world have been studying and planning workforce supply and strategies, such as the European Union's Joint Action on Health Workforce Planning and Forecasting,[2] Australian Medical Advisory Committee,[3] Netherlands Advisory Committee on Medical Manpower Planning, Belgian Health Workforce Planning Unit, International Medical Workforce Collaborative and others. The task of determining the distribution, specialist types, quantity and quality of healthcare professionals has been started around the world, in order to plan the future healthcare workforce.[4-6]

The training process for healthcare professionals is very long and complex. For physicians, the time span from the beginning of medical school until entering the labor market may be more than 12 years.[7] Understanding the specialization processes and distribution of medical specialists seems to be essential for good workforce planning.

Aside from all the general complexity, there are different mechanisms for training medical specialists in Brazil. There are also singular regulations for the accreditation process of medical specialization:[8,9]

1) Medical Residency. This is considered to be the gold standard method with nationally unified laws, rules and criteria. Medical residency is administered by the National Medical Residency Committee (Comissão Nacional de Residência Médica, CNRM), which is located within the Ministry of Education and is composed of representatives of the Ministry of Education, Ministry of Health, Brazilian Medical Association, Medical Union, Federal Medical Council, National Residents Association, Municipal Health Departments and State Health Departments, thus constituting the plenary body of the CNRM.
2) Medical Specialization Courses. These are courses accredited by specialist medical societies that are used to train new specialists. The models for such courses have variable criteria that are approved by the Scientific Council of the Brazilian Medical Association. This training process historically has had a significant role in Brazil. It usually involves the same length of training and part of the content of medical residency programs. The specialist medical societies apply an evaluation process at the end of the training period, although with variable criteria.

After new graduates receive the formal degree of physician, Brazilian law allows them to practice any medical specialty, as long as they feel able to do so. After a validated and well-documented period of a few years of practice in well-reputed services, under the supervision of experts, physicians can apply to take tests administered by the Brazilian Medical Association, in order to receive a certificate in a specialty. The same certificate is validated at the end of medical residency training.

Regardless of the path taken, physicians' certificates need to be registered at the Federal Medical Council, which, according to a specific law,[10] has the power to regulate and supervise medical practice.[11]

Even today, the Brazilian healthcare and educational authorities are still trying to identify the real number of specialists in the country and the actual requirements in each of the 53 medical specialties recognized in this country,[12] in accordance with epidemiological data and international parameters. It is also necessary to bring training methods together through recognizing historical Brazilian medical practices and specialist training processes.

The CNRM[13,14] has started to work in this direction with the specialist medical associations. The intention was to unify the training process, so as to avoid the possibility that different learning material (knowledge, skills and attitudes) might be provided for the same specialist qualification. Among the 53 recognized Brazilian medical specialties, neurosurgery was chosen for the pilot project of this study.

Neurosurgery was chosen because the Brazilian Society of Neurosurgery (Sociedade Brasileira de Neurocirurgia, SBN) was willing to participate and because access to its Neurosurgery Assessment Committee was facilitated. The SBN has a well-organized evaluation process that covers institutions, their residency programs and residents. It was taken into account that it is virtually impossible to practice neurosurgery without formal training and official recognition.

The CNRM and SBN started by working together, planning an assessment tool and visiting neurosurgery residency programs and neurosurgery services throughout the country.

OBJECTIVE

This study had the aim of assessing the current situation of medical residency programs in neurosurgery in Brazil, in the light of the partnership between the CNRM and SBN. It also aimed to analyze the locoregional distribution of medical residency programs within neurosurgery, the distribution of specialists in this field and the current situation now that the SBN-CNRM collaboration has come into practice.

METHODS

This study began with a review of the available scientific literature, through searching regional databases (Lilacs, SciELO and Bireme) and global databases (PubMed and Web of Science) with regard to the external medical residency evaluation process implemented by government bodies, professional associations, scientific societies, etc. In addition, any available articles and

legislation relating to evaluation, regulation and supervision that had been published by government bodies such as the Ministries of Health and Education, or by medical associations, the Federal Medical Council or other similar entities, were also included.

Focusing on the quality of neurosurgical residency, a single assessment instrument was developed by the CNRM and SBN in relation to the supervised in-service educational process, which aimed to investigate the following factors: infrastructure and characteristics of the institution; educational program; care profile; staff qualifications; whether the staff worked exclusively for the institution in question; clinical demands (number and variety of cases in accordance with the competencies to be developed over the period of the residency program); and development (apprenticeship) of medical residents.

The process of on-site educational evaluation took place as follows:

1) The instrument was sent to the institutions to be evaluated in accordance with criteria that had been established jointly by CNRM and SBN.
2) No more than two weeks after the instrument had been sent out, institutions across the country were visited by at least two appraisers (at least one person from CNRM and another from SBN), in accordance with a predetermined schedule. The evaluation team assessed the conditions of the wards, outpatient clinics, surgical center, radiological unit, hemodynamic unit, laboratory, emergency room, intensive care unit, all necessary tools (including microscopes), numbers and types of operations performed within the last six months, library provision, access to electronic libraries and compliance with theoretical programs and legislation.
3) The evaluation team held meetings separately with the management of each institution, the coordinators and supervisors of the medical residency programs and the medical residents for the purpose of ascertaining the strengths and weaknesses of the program.
4) A final report was produced by the evaluation team.
5) The reports thus produced were analyzed by a CNRM technical council, which deliberated on corrective measures to be proposed for residency programs.
6) The plenary body of the CNRM deliberated on the measures suggested by the technical council.
7) The institutions were notified of the measures that needed to be implemented over a certain period of time that was set by the plenary body of the CNRM.
8) Compliance with the changes was verified at the end of the period proposed by the plenary body of the CNRM.

We evaluated all the assessments that were made and all the opinions issued by the CNRM technical council, and attempted to check their impact on the recent history of each program and the consequences for the healthcare provided at the institution and for medical education decisions.

Meetings between representatives from SBN and CNRM were held to establish goals and work processes; to unify criteria and evaluation instruments; and to train the evaluation team. These meetings were held between April 2010 and February 2011.

The assessment visits took place between April 2011 and January 2014. Over this period, and until April 2014, the CNRM technical council analyzed the reports, the CNRM plenary body deliberated on the measures suggested and the institutions were notified of the actions to be implemented within the prescribed period. Finally, the changes implemented were checked at the end of the proposed period.

RESULTS

Brazil has 26 states and one federal district. It was found that seven states do not have any neurosurgery programs: Acre, Amapá, Rondônia and Roraima (northern region); and Maranhão, Paraíba and Piauí (northeastern region). These seven states without neurosurgery programs correspond to regions with low Human Development Index (HDI).[15]

Neurosurgeons are distributed through the regions of Brazil: 94 in the north, 245 in the northeast, 171 in the center-west, 1197 in the southeast and 362 in the south, as demonstrated in previous studies.[16,17] If these numbers are correlated with population sizes, the shortages of neurosurgeons can be better understood. The number of neurosurgeons per 100,000 inhabitants, according to Brazilian region, as defined by the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE, 2010),[18] is as follows: 0.59 in the north, 0.47 in the northeast, 1.49 in the southeast, 1.40 in the south and 1.22 in the center-west. The average number of neurosurgeons per 100,000 inhabitants for the whole country was 1.09.

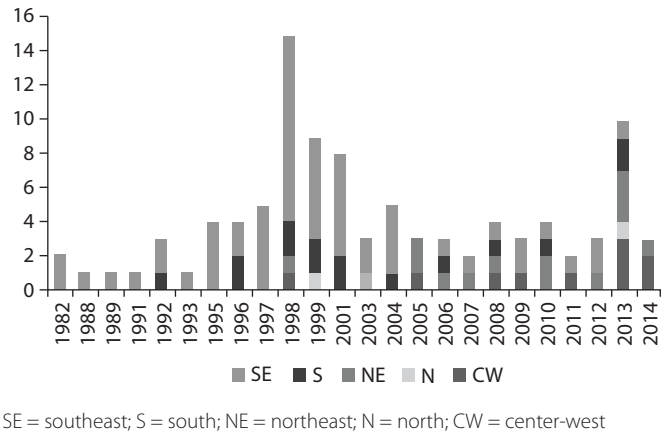
Across the country, there were 154 vacancies for admission to medical residency programs in neurosurgery, distributed in 105 programs. Again dividing Brazil according to regions, the number of medical residency programs in neurosurgery per 100,000 inhabitants was 0.03 in the north, 0.03 in the northeast, 0.12 in the southeast, 0.10 in the south and 0.06 in the center-west. The average number of medical residency programs in neurosurgery per 100,000 inhabitants for the whole country was 0.08.[18] Seventeen new neurosurgery programs were created during the study period and represented 14.6% of the total. Three were in the south, four in the southeast, three in the northeast, four in the center-west and three in the north.

Figure 1 represents the evolution of neurosurgery medical residency programs (NMRPs) installed in the five Brazilian regions over the last 30 years (i.e. since 1982). The shades of gray

show that in the 1980s and 1990s, there was a heavy concentration of NMRPs in the southeastern and southern regions. Over that period, new program startups in other regions were exceptional. From 1999 to 2003, new NMRPs emerged in other regions. Over the past three years, the distribution of neurosurgery residency positions according to region has started to change. In particular, there was greater diversity in NMRP startups in 2012, with good responses in the northeastern and central-western regions.

The CNRM recognizes that 127 neurosurgery programs have existed historically. At the time of the present evaluation process, there were 105 programs. Twenty-three neurosurgery programs had been canceled before the data analysis process took place, or were canceled during it.

After the assessment, it was possible to approve 28 NMRPs without any restrictions, corresponding to 26.7% of the total. Twenty-two of these programs are located in the southeast, five in the south and one in the north. **Table 1** shows the situation of the 105 neurosurgery programs after the CNRM/SBN evaluation. Thirty-seven programs were placed under supervision for correction of irregularities (**Table 1**): eight in the south, twenty in the southeast, five in the northeast, and two each in the center-west and north. Four neurosurgery programs had to be closed immediately due to lack of appropriate conditions for teaching and medical care: three in the southeast and one in the northeast. For one program that was placed under supervision by the technical board, corrections were made quickly and it was approved by the final CNRM plenary session. Four programs continued to be out of date by the end of the period covered by this study. Fourteen were still waiting for assessment visits and no impact or results can be presented because they were first visited just a few weeks before the project began and could not be evaluated within five years.



SE = southeast; S = south; NE = northeast; N = north; CW = center-west

Figure 1. Neurosurgery residency training programs installed over the last 30 years in the five Brazilian regions.

The most common problems found in the final reports of the evaluation, technical papers and CNRM plenary body are shown in **Tables 2** and **3**. These problems observed in the results can be divided into two groups:

- Service faults (structure, processes and outcomes), subdivided into the classical triad of healthcare service assessment drawn up by Donabedian,[18,19] here with 19 different kinds of important problems found.
- Learning faults, concerning information and assessments used by the Ministry of Education to analyze medical residency, with 12 different important features found.

We defined structure as the materials (infrastructure, equipment and supplies) needed to conduct the residency program. Processes were defined as the relationship between human resource management, learning and healthcare. The results represented the ability and efficiency of surgery and clinical care.

The main problems found within teaching and learning related to deficiencies in internships, but there were also shortages of supervision and theoretical programs. **Table 3** summarizes the teaching and learning problems identified during the CNRM/SBN evaluation.

DISCUSSION

There is huge inequity with regard to economics, culture, health, educational performance and access, HDI and other factors among the the different regions.[15,20] It is known that economics and HDI are linked to human capital, development and empowerment.[21] There is a relationship between HDI and the numbers of neurosurgery programs and neurosurgeons. Neurosurgeons and neurosurgery residency vacancies are concentrated in the regions with best HDI. There seems to be a "snowball" of growth in inequity. Worse HDI correlates with services that have poor structure. This scenario is unattractive,

Table 1. Situation of the 105 neurosurgery programs after evaluation by the National Medical Residency Committee (Comissão Nacional de Residência Médica, CNRM) and the Brazilian Society of Neurosurgery (Sociedade Brasileira de Neurocirurgia, SBN)

Classification impact	Number of programs
Approved	28
Changes made before final evaluation	1
Closed	4
Corrections and supervision	37
New program	17
Out of date	4
Awaiting visit	14
Total	**105**

Table 2. The most common problems found in the final reports from the evaluation, technical papers and National Medical Residency Committee (Comissão Nacional de Residência Médica, CNRM) plenary body regarding services

Healthcare outcomes	Brazilian regions (number of neurosurgery programs)				
	NE (9)	CW (2)	SE (23)	S (9)	Total (43)
Lack of information about operations	1	0	6	0	7
Annual number of surgical procedures less than 300	4	0	6	1	11
Insufficient intensive care beds	1	0	1	0	2
Low number of pediatric procedures	2	0	5	5	12
Low number of vascular procedures	1	0	4	2	7
Low number of functional procedures	1	0	2	4	7
Low number of tumoral procedures	0	0	1	3	4
Low number of spinal procedures	1	0	0	1	2
Low number of peripheral nerve procedures	0	0	1	1	2
Lack or deficiency of outpatient clinic	1	0	1	1	3
Structure	**NE**	**CW**	**SE**	**S**	**Total**
Lack or deficiency of materials to perform surgery	2	0	4	2	8
Lack or insufficiency of neuroimaging resources	0	0	2	1	3
Lack of basic library	1	0	0	0	1
Process	**NE**	**CW**	**SE**	**S**	**Total**
Lack of human resources or materials, or difficulty in scheduling the operating room	2	1	0	0	3
Lack of diary for making appointments with physician team	1	0	1	0	2
Medical residents doing shifts at a long distance away	2	0	4	0	6
Internships and weekly agenda incorrect, according to CNRM rules	1	1	9	4	15
Lack of minimum working conditions and disregard of the number of hours/week per resident	1	1	8	3	13
Lack of institutional organizational documentation	0	0	2	0	2

NE = northeast; CW = center-west; SE = southeast; S = south.

Table 3. The most common problems found in the final reports from the evaluation, technical papers and National Medical Residency Committee (Comissão Nacional de Residência Médica, CNRM) plenary body regarding education

Teaching and learning outcomes	Brazilian regions				
	NE	CW	SE	S	Total
Lack or deficiency of emergency service internship	1	0	3	1	5
Lack or deficiency of supervision or preceptorship	5	1	8	2	16
Lack or deficiency of neurology internship	1	0	3	5	9
Lack or deficiency of neuroanatomy and experimental microsurgery internship	2	0	4	3	9
Lack or deficiency of theoretical, teaching or didactic program	1	1	5	3	10
Lack or deficiency of clinical visits	1	0	0	1	2
Lack or deficiency of anatomical/clinical, pathological/clinical or radiological/clinical sessions	1	0	4	1	6
Lack or deficiency of clinical case discussions	1	0	2	1	4
Excess of residents to be trained in relation to the service features	1	0	3	0	4
Lack or deficiency of interventional neuroradiology internship	0	0	6	0	6
Lack or deficiency of resident assessment	0	0	4	1	5
Lack or deficiency of intensive care unit internship	0	0	2	0	2

NE = northeast; CW = center-west; SE = southeast; S = south.

and sometimes makes it impossible to practice neurosurgery specialization. The lack of specialists and structure make residency positions impossible, or even undesirable. Without medical residency training, there will be fewer specialists and less structure.[22]

There has been a federal government policy to induce residency programs since 2009, including for neurosurgery. This policy, called "ProResidência", is an important initiative by the Ministries of Health and Education.[23] ProResidência provides financial input from the Ministry of Health for residency. It is also responsible for putting into practice some discussion on planning and provision of doctors (generalists and specialists), and on the requirements of the population. The choice among the medical specialties for which residency programs might be induced is made according to the difficulty in hiring specific specialists in both the public and the private healthcare sectors.[24]

Other strategies are being implemented, such as supervision and assistance between institutions that want to improve their programs or start new ones and experienced universities.[25] This strategy is a tentative government initiative, and its results have not yet been assessed. It is known as "matriciamento" (matrix support)[26] and was designed to reformulate the process of health-care work and used also for teaching and learning.

CONCLUSION

Only about a quarter (26%) of the programs were immediately approved through this evaluation project. The evaluation team from the CNRM was well prepared to address the educational and legal aspects of medical residency in general, and this knowledge was brought to bear in these joint evaluations. The evaluations team of the SBN added value with regard to developing the content of the residency programs and technical issues relevant to the specialty.

CNRM and SBN have unified their evaluation criteria, showing very complex results, with large numbers of needs and weaknesses. It seems clear that although the isolated and parallel evaluation processes used in Brazil today are important, unification makes a difference with regard to improving the quality of teaching, clinical services and future medical practice.

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Sources of funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) Scholarship process number: 6103-14-6
Conflict of interest: None

Date of first submission: September 8, 2014
Last received: November 18, 2014
Accepted: November 25, 2014

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DOI: 10.1590/1516-3180.2015.00080108

Development of clinical reasoning in an undergraduate medical program at a Brazilian university

Desenvolvimento do raciocínio clínico na graduação médica em uma universidade brasileira

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KEY WORDS:
Qualitative research.
Students, medical.
Education, medical.
Curriculum.
Cognition.

PALAVRAS-CHAVE:
Pesquisa qualitativa.
Estudantes de medicina.
Educação médica.
Currículo.
Cognição.

ABSTRACT

CONTEXT AND OBJECTIVE: The cognitive processes relating to the development of clinical reasoning are only partially understood, which explains the difficulties in teaching this skill in medical courses. This study aimed to understand how clinical reasoning develops among undergraduate medical students.

DESIGN AND SETTING: Quantitative and qualitative exploratory descriptive study conducted at the medical school of Universidade Federal de Goiás.

METHODS: The focus group technique was used among 40 students who participated in five focus groups, with eight students from each year, from the first to fifth year of the medical school program. The material was subjected to content analysis in categories, and was subsequently quantified and subjected to descriptive statistical analysis and chi-square test for inferential statistics.

RESULTS: The content of the students' statements was divided into two categories: **clinical reasoning** — in the preclinical phase, clinical reasoning was based on knowledge of basic medical science and in the clinical phase, there was a change to pattern recognition; **knowledge of basic medical science** — 80.6% of the students recognized its use, but they stated that they only used it in difficult cases.

CONCLUSION: In the preclinical phase, in a medical school with a traditional curriculum, clinical reasoning depends on the knowledge acquired from basic medical science, while in the clinical phase, it becomes based on pattern recognition.

RESUMO

CONTEXTO E OBJETIVO: Tem-se compreensão parcial dos processos cognitivos relacionados ao desenvolvimento do raciocínio clínico, o que justifica as dificuldades no ensino dessa competência nos cursos de medicina. Este estudo tem como objetivo compreender como se desenvolve o raciocínio clínico em acadêmicos de medicina.

TIPO DE ESTUDO E LOCAL: Pesquisa descritiva exploratória quantitativa e qualitativa, realizada na Faculdade de Medicina da Universidade Federal de Goiás.

MÉTODOS: A técnica de grupos focais foi utilizada entre 40 acadêmicos, que participaram de cinco grupos focais, com oito acadêmicos de cada ano, do primeiro ao quinto ano do curso médico. O material foi submetido a análise de conteúdo por categorias, posteriormente quantificado e submetido a análise estatística descritiva e teste de qui-quadrado para estatística inferencial.

RESULTADOS: O conteúdo das falas dos participantes foi dividido em duas categorias: **raciocínio clínico** — na fase pré-clínica, o raciocínio clínico é baseado no conhecimento das disciplinas básicas e, na fase clínica, há uma mudança para o reconhecimento de padrões; **conhecimento das disciplinas básicas** — 80,6% percebem sua utilização, porém assinalam que o usam apenas em casos difíceis.

CONCLUSÃO: Na fase pré-clínica, em uma escola médica com currículo tradicional, o raciocínio clínico é dependente dos conhecimentos adquiridos nas disciplinas básicas e, na fase clínica, passa para o reconhecimento de padrões.

INTRODUCTION

Medical training is based on construction of a cognitive structure.[1,2] The cognitive processes relating to clinical reasoning are only partially understood.[3-6] The ability to memorize the contents of both basic science and large sets of clinical cases does not provide experience.[7] Rather, experience depends on the ability to memorize the content together with supervised professional practice.[1,8]

Two fundamental approaches have been recognized for reasoning: intuitive and analytical reasoning,[1,5,9-12] which present different components. Intuitive reasoning involves pattern recognition (through categorization, a theory of disease scripts or a mental models theory), intuition and heuristics; while analytical reasoning involves hypothetical-deductive and probabilistic approaches.

Pattern recognition implies speed. The clinical reasoning of experienced students does not involve testing hypotheses in common situations. The theory of pattern recognition aims to explain how human beings understand the world.[13] Memory involves encoding cognitive structures.[14] A pattern determines what is normal and what is a variation of the norm.[13,15]

Medical students recognize signs and symptoms in a patient context when they perform their activities.[7] These perceptions activate recognition of disease patterns, with which they interpret the information about the characteristics of that situation.[9,11,13,15,16] The patterns present limited knowledge about the causal mechanisms but a large amount of information about the signs and symptoms of diseases. By applying these cognitive structures, the students quickly generate diagnoses for routine problems.[17]

Intuition can change decisions and lead to better performance than analytical deliberation. Students are advised not to trust their intuition, so as to avoid reasoning errors. Although this process is present and influences physician decision-making, it represents only part of the whole process.[18]

Heuristics is the process that aims to simplify complex reasoning relating to diagnoses that meet the established requirements. These cognitive shortcuts depend on previous knowledge. Heuristics is quick decision-making.[19]

The **hypothetical-deductive approach** can also be called the critical method, or Popper's method of trial and error. To solve problems, the students use a cognitive method similar to the scientific method, or approaches used by detectives in addressing a crime.[20]

Several hypotheses are generated when a student addresses a real-world problem. Each hypothesis is sequentially tested, in order to be confirmed or eliminated, and then the final decision is made.[9,11] Therefore, knowledge of basic medical science is important for establishing the cognitive structures and a relationship between the pathophysiology of the disease and the clinical characteristics of patients.[1,7,21] This **probabilistic** approach implies that the analysis of clinical problems should be based on a Bayesian approach, i.e. systematic use of the Bayes theorem in which the post and pre-test probabilities (i.e. the prevalence of the disease) are correlated. The students may use health statistics in association with their initial clinical experience.[22] In fact, only a small percentage of students use a Bayesian approach, and most of them use an informal method of data review.

A student's level of knowledge changes with practice.[5,11,23] In diagnosing common problems, experienced students tend to use quick and automatic reasoning (pattern recognition).[5,14,21,24] In cases of more complex problems in which there is no recognized pattern,[15] an analytical/reflective approach (hypothetical-deductive method) that uses the stored knowledge of basic science is triggered. Automatic reasoning tends to be efficient in routine situations,[14,24] but it can lead to mistakes when the problems are complex.[21,24]

The understanding of learning has advanced considerably over recent decades, thus affecting various teaching and learning strategies. Recently, not only the curricula but also the scenarios and strategies of teaching and learning have been restructured.[25] Medical practice requires multiple skills,[26] which include clinical reasoning.[6] The difficulties in teaching this skill are due to lack of knowledge about its development.[5] Knowledge of the process of developing clinical reasoning is a requirement for its comprehension and for improvement of medical training.

OBJECTIVE

This study aimed to understand the development of the process used for clinical reasoning among first to fifth-year undergraduate students at a medical school with a traditional curriculum in a federal public institution of higher education in Brazil.

METHODS

A cross-sectional, descriptive, exploratory, qualitative and quantitative study was conducted. The focus group technique was used to gather data. This study was approved by the UFG (Federal University of Goiás) Ethics Committee, under number 176/12.

The medical course that was the subject of this study had a traditional curriculum and was offered at a medical school located in the center-west of Brazil. Every year, 110 new undergraduate students begin a six-year course that is divided into a preclinical phase (two years) and a clinical phase (four years) that includes two years of supervised training.

The participants were recruited at the institution investigated. First to fifth-year undergraduate students older than 18 years who were enrolled in the medical course and who agreed to participate by signing a free and informed consent statement were invited to participate in the study. The following undergraduate students were excluded: those younger than 18 years; those with enrolment in the medical course that had not been regularized in the medical school's office; those whose year of enrolment

was not clear; those who refused to participate, fearing embarrassment that could occur through the study; and sixth-year undergraduate students, because they were receiving training away from the university campus.

A total of 40 undergraduate students were analyzed. They participated in five focus groups (eight students per academic year), with a focus group for each academic year of the course (first to fifth year). The focus groups were conducted in the classrooms, at predetermined times that avoided conflicts with the academic schedules, and lasted ninety minutes. A script with three questions (**Chart 1**) guided the discussion in the focus groups. The meetings were recorded and transcribed verbatim.

The material was evaluated by means of content analysis. The data were analyzed according to categories. The response units emerged within the categories, which described the main ideas discussed during the meetings. These ideas were quantified in each focus group. The quantification of response units was statistically analyzed.

Microsoft Excel 2007 and SPSS for Windows version 16.0 were used for statistical analysis. To evaluate differences in how clinical reasoning was organized and in perceptions of the use of basic medical science between the preclinical and clinical phases, the chi-squared test was used, with a significance level of 5% ($P < 0.05$).

RESULTS

The content of the participants' statements in the focus groups was divided into the categories of clinical reasoning and knowledge of basic medical science.

Clinical reasoning

The majority of the undergraduate students in the preclinical phase developed their clinical reasoning based on knowledge acquired from basic medical science, using a line of reasoning based on knowledge about organs or body systems. This result was observed in 27/29 (93.1%) of the students' statements in the preclinical phase. Some representative statements included "*We verify the symptoms, and then we observe the main system affected*" and "*I observed a group of symptoms and sought a system.*"

The clinical reasoning gradually changed in the statements of the undergraduate students during the clinical phase. The third and fourth-year undergraduate students still used the earlier knowledge of basic science, which was observed in 10/16 (62.5%) of the third-year undergraduate students' statements and in 19/25 (76%) of the fourth-year undergraduate students' statements: "*It comes from something that you already knew. The observations of signs and symptoms give you a sense of what organ or system is affected*"; "*I always reason from previous cases or something I have read*"; and "*I generate a diagnostic hypothesis based on knowledge of something that I have previously studied.*"

Chart 1. Key questions for the focus groups

1) Describe how your formulation of clinical hypotheses is processed.
2) Have you used knowledge from the basic disciplines in the formulation of clinical hypotheses?
3) If you have not used knowledge from the basic disciplines, what do you think the reason was ?

The results showed that the use of automatic reasoning developed over the third, fourth and fifth years of medical school. Thus, automatic reasoning was observed in 4/16 (25%), in 6/25 (24%) and in 11/14 (78.5%) of the statements of third, fourth and fifth-year undergraduate students, respectively: "*The first hypothesis that comes from automatic reasoning is important*"; "*It is an automatic thing, and you do not even notice it*"; and "*It just appeared.*"

In the preclinical phase, the clinical reasoning was based on previous knowledge obtained from basic medical science, while in the clinical phase, it became automatic. The difference in the frequencies of these types of statements was statistically significant between the phases ($P < 0.001$).

Knowledge of basic medical science

A total of 50/62 (80.6%) of the students' statements indicated that they used basic medical science in their clinical reasoning, while this was not observed in 12/62 (19.4%). Their statements included the following: "*From the standpoint of what is normal, something that is not happening normally should be an alteration of the normal; if you do not know what is normal, which is taught within basic medical science, you will not be able to understand what caused the disorder*"; and "*We use what we retain; things that are important.*" No statistically significant difference in the perception of the use of basic medical science for reasoning was observed between the preclinical and clinical phases ($P = 0.95$).

The statements of the students who did not use basic medical science included: "*I think we do not use most of the basic medical science*"; "*We do not consciously use it*"; "*The entire range of knowledge acquired over the first two years of the course are not used in practice*"; and "*I speak for myself, but I do not use it when I have to reason.*"

Students in all the years assessed stated that they always went back to the basic medical science in difficult cases: "*If the case is very difficult, I search for it in the areas of anatomy, biochemistry and histology to see if I can find some information*" (first-year); "*You go back to the basic medical science when you read a difficult case*" (third-year); "*I think about less common diseases; I reassess the systems. I use the basic medical science to interpret the findings*" (fourth-year); and "*We use the basic medical science when the case is difficult*" (fifth-year).

DISCUSSION

Clinical reasoning

The development of clinical reasoning observed in the present study is in agreement with the current theories of clinical reasoning: the hypothetical-deductive method and pattern recognition (scripts).[4,9,11,16,23,27-31] The novelty of the present study is the better comprehension that it provides regarding the temporality of the students' progress within the academic curriculum; i.e. the change in undergraduate medical students' clinical reasoning stemming from their interaction with patients.

However, this study was not able to explain whether the migration from basic knowledge to pattern recognition occurs uniformly among students, or whether it is predominantly in the best students, because the students participated in the focus groups together and their statements do not have this information.

Many of our observations can be explained by the "Taxonomy of educational objectives" proposed by Bloom.[32] There are three specific domains in this model: cognitive, affective and psychomotor. The cognitive and psychomotor domains involve acquisition of knowledge, intellectual development and physical ability. They include recognition of specific facts, standard procedures and concepts that stimulate intellectual development. The affective domain relates to values and attitudes.[33]

The cognitive domain comprises a) **remembering:** recognizing and reproducing ideas and contents; b) **understanding:** establishing a connection between the new information and previously acquired knowledge; c) **applying:** using a procedure in a specific or new situation; d) **analyzing:** understanding the interrelationship between the parts; e) **evaluating:** making judgments based on criteria; and f) **creating:** a new vision, a new solution.[33]

Through analyzing Bloom's taxonomy, it can be inferred that the students in the preclinical phase can remember, understand and apply the knowledge acquired within basic medical science (organ systems). However, they have difficulty in analyzing and evaluating because they have not yet attended the courses that address clinical signs and symptoms. Therefore, hypothetical-deductive reasoning limited to knowledge of body systems is developed. Regarding the final category (creating), which was interpreted as diagnosis in the present study, it is very limited among students at this point of the medical course.

Also based on Bloom's taxonomy, it can be inferred that the students of the clinical phase are already able to remember, understand, apply, analyze, evaluate and create; and that they gradually become able to complete a chain of hypothetical-deductive diagnostic reasoning or pattern recognition, depending on their experience.

However, it needs to be considered whether the migration from basic science to pattern recognition as the basis for reasoning might merely reflect the fact that students are progressively exposed to more clinically oriented content as the course advances.

It is believed that students will gradually assimilate the material and knowledge that they need through a mechanism known as knowledge integration.[2,7,34] Integration of the knowledge obtained from basic medical science occurs due to repeated application of this knowledge within clinical practice environments, as an easier way to access the reasoning structures.[1,2,7,34] Undergraduate students acquire the necessary biological knowledge during the preclinical phase of the medical course.[7] During the clinical phase, they interact with patients and then apply the acquired knowledge. Thus, application of this knowledge associated with acquisition of practical knowledge begins to link the signs and symptoms to the diagnostic hypotheses. When applied to clinical reasoning, this link leads to integration of clinical and biomedical knowledge, thus concluding the process.[1,2,7,34]

Three stages in the development of clinical reasoning have been described: acquisition of knowledge of basic medical science; experience acquired through contact with patients; and integration of theoretical knowledge.[7] Therefore, when third, fourth and fifth-year students start to come into contact with patients, they progressively exhibit the integration process and gradual formation of their scripts.[13]

The students' statements demonstrated that during the preclinical and clinical phases, they followed different lines of reasoning to solve problems and that there was no single way to do this. Several cognitive actions occur, starting from when a clinical meeting begins: clinical knowledge is activated; scripts are mobilized and enriched; and integrated knowledge is accessed. These processes occur together and are controlled by meta-cognition, thus indicating that clinical reasoning is not a linear process but rather, a sequence of steps.[3,26]

Knowledge of basic medical science

Our observations are in agreement with the current theories, which state that knowledge obtained from basic medical science is used in situations where pattern recognition (scripts) has not yet developed. In these cases, students use basic knowledge to understand the situation and find relevant hypotheses through a causal chain of reasoning.[13]

The students in the preclinical phase who had not yet developed pattern recognition (scripts) presented analytical reasoning based on their knowledge obtained from basic medical science. In contrast, students in the clinical phase used faster and non-analytical ways of reasoning with pattern recognition that included knowledge retrieval. This develops through integration of clinical knowledge, and in difficult cases, they still called

upon their knowledge of basic medical science.[5] Therefore, clinical reasoning functions as a cognitive link, through establishing a process in which knowledge of basic medical science is used as a bridge for the transition to the clinical phase.[2]

The present study, which was conducted among students, has some limitations. This study did not include the sixth-year undergraduate students because of difficulty in gaining access to them, given that they were undergoing training outside of the university's medical school. These students would probably have higher levels of knowledge which would make the data more robust. The qualitative method is characterized by empiricism and progressive systematization until an understanding of the internal logic of a group is achieved. We sought to impose methodological rigor; however, in the data interpretation step, we might have attained only partial understanding of some of the participants' ideas, thereby involuntarily resulting in small distortions of the data.

CONCLUSION

In the preclinical phase of undergraduate medical education, clinical reasoning still depends on knowledge from basic medical science. In the clinical phase, when the students start to interact with patients, the pattern-recognition type of reasoning starts to develop.

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Sources of funding: None
Conflict of interest: None.

Date of first submission: January 13, 2015
Last received: May 25, 2015
Accepted: August 1, 2015

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DOI: 10.1590/1516-3180.2015.00100108

Script concordance test in medical schools in Brazil: possibilities and limitations

Teste de concordância de *script* nas escolas médicas no Brasil: possibilidades e limitações

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KEY WORDS:
Educational measurement.
Students, medical.
Education, medical.
Curriculum.
Cognition.

PALAVRAS-CHAVE
Avaliação educacional.
Estudantes de medicina.
Educação médica.
Currículo.
Cognição.

ABSTRACT

CONTEXT AND OBJECTIVE: Routine use of the script concordance test (SCT) is not common in Brazilian universities. This study aimed to analyze application of the SCT in the medical school of a Brazilian university.

DESIGN AND SETTING: Quantitative, analytical and descriptive study in the medical school of a Brazilian university.

METHODS: A total of 159/550 students participated. The test comprised ten clinical cases within internal medicine, with five items per case, rated on a five-point Likert scale. The test was scored in accordance with a marking key that had been validated by a reference panel.

RESULTS: In the pre-clinical and clinical phases, the mean scores were 51.6% and 63.4% of the maximum possible scores, respectively. Comparison of the means of the responses among all the years showed that there were significant differences in 40% of the items. The panel marked all the possible answers in five items, while in one item, all the panelists marked a single answer. Cronbach's alpha was 0.64. The results indicated that the more senior students performed better. Construction of an SCT with discriminative questions was not easy. The low reliability index may have occurred due to: a) problems with the construction of the questions; b) limitations of the reference panel; and/or c) the scoring key.

CONCLUSION: This instrument is very difficult to construct, apply and correct. These difficulties may make application of an SCT as an assessment method unfeasible in units with limited resources.

RESUMO

CONTEXTO E OBJETIVO: O uso rotineiro do teste de concordância de *script* (SCT) não é comum nas universidades brasileiras. Este estudo objetiva analisar a aplicação do SCT na graduação em medicina de uma universidade brasileira.

TIPO DE ESTUDO E LOCAL: Estudo quantitativo, analítico e descritivo na faculdade de medicina de uma universidade brasileira.

MÉTODOS: Participaram 159/550 acadêmicos. O teste possuía dez casos clínicos em Medicina Interna, cada caso com cinco itens, classificados em uma escala de Likert de cinco pontos. O teste foi corrigido conforme gabarito validado por um painel de referência.

RESULTADOS: Na fase pré-clínica, a média foi 51,6% e, na fase clínica, 63,4% da nota máxima. Comparando a média das respostas entre todos os anos, obteve-se diferença significante em 40% dos itens. O painel demarcou todas as possiblidades em cinco itens e em um item todos marcaram uma resposta. O índice alfa de Cronbach foi de 0,64. Demonstramos que os mais graduados obtiveram desempenho melhor. A construção de um SCT com questões discriminativas não foi fácil. O índice de confiabilidade baixo pode ter acontecido por: a) problemas na construção das questões; b) limitações do painel de referência; c) sistema de pontuação.

CONCLUSÕES: O instrumento é de grande dificuldade de construção, aplicação e correção. Essas dificuldades podem inviabilizar a sua aplicação como método de avaliação em unidades com recursos limitados.

INTRODUCTION

The written tests most commonly used to assess student learning in medical education are multiple-choice tests[1] The assessment capacity of these tests fails in contexts of uncertainties. A standardized assessment based on the cognitive theory of scripts or the script concordance test (SCT) may be an alternative for analyzing decision-making in these situations.[1,2] The general trend in medical education has been to rely less on written test formats and increasingly on performance-based assessments (PBA).[3] These assessments document behavior in solving problems in simulated cases.[3]

The SCT is intended to evaluate the information interpretation process.[4] The instrument has been developed in various educational settings and in different countries and languages and is based on written presentation of short clinical cases, followed by a choice of diagnostic and therapeutic decisions.[1,5-13] Routine use of the SCT is not common in Brazilian universities.

OBJECTIVE

This study aimed to analyze application (construction and results) of the SCT assessment tool among medical students in the first to fifth years of training at a Brazilian university.

METHODS

This was a quantitative, analytical and descriptive study at the School of Medicine, Federal University of Goiás (Faculdade de Medicina da Universidade Federal de Goiás, FM-UFG). This study was approved by the UFG Ethics Committee under number 176/12.

All 550 students from the first to the fifth year of the undergraduate program were invited to take an SCT. The recruitment of participants took place at FM-UFG by means of an invitation to all students who met the inclusion criteria. Students over 18 years of age who were enrolled and who signed the consent form were included. Students whose native language was not Portuguese and sixth-year students were excluded. The latter were excluded because of difficulty in accessing groups that were attending training courses outside of the institution.

The SCT was applied on previously scheduled days, on one day for each year of the program, on the FM-UFG premises. The test was completed by each student over a 90-minute period, regardless of year, and was the same for all the study subjects.

The test was developed by the researchers using 10 short clinical cases within internal medicine involving diagnostic questions on the following topics: acute myocardial infarction, pleural effusion, pneumonia, pulmonary embolism, malignant stomach tumor, cirrhosis of the liver, gastroesophageal reflux disease, congestive heart failure, acute renal failure and secondary hyperparathyroidism. There were five items for each of the ten clinical cases, thus yielding a total of 50 items. The clinical scenarios were followed by a series of questions, which were presented in three parts. The first part ("if you were thinking...") contained a relevant diagnosis. The second part ("and then you find...") presented a new clinical finding, such as a physical sign, a pre-existing condition, an imaging study or laboratory test result. The third part ("this option would become...") displayed an answer in a Likert scale format, in which the subject quantified how much influence the new information (second part of the question) would have on what he was thinking (first part of the question). The answers followed a five-point Likert scale that captured the participants' decisions (**Table 1**).[2]

The students had to decide what effect the new discovery (second part of the question) had on the state of the option cited in the directions (first part of the question), whether positive, negative or neutral, and the intensity of this effect using the Likert scale. The Likert scale structure was the same for the entire test, with negative values on the left, 0 in the neutral position and positive values on the right (-2: very unlikely; -1: unlikely; 0: neither likely nor unlikely; +1: likely; and +2: very likely) (**Table 1**).

The students were instructed not to answer questions for which they did not understand the answers, and these questions were given a score of 0 in the overall rating.

The test was scored in accordance with a marking key that had been validated by a reference panel made up of 10 professors of the FM-UFG Department of Clinical Medicine. The professors were invited to volunteer because they were experts in various areas of medical knowledge and belonged to the FM-UFG Department of Clinical Medicine. Three were cardiologists; two were nephrologists; one was a pulmonologist; one was a hematologist; one was a gastroenterologist; one was from the Intensive Care Unit; and one was from the Immunology Department. Scoring the SCT involved comparing the responses provided by the participants with those of the reference panel.

Table 1. Example of one question used in the script concordance test

"A 33-year-old male presenting with heartburn for 30 days and occasional regurgitation. Social drinker"		
If you were thinking of	**And then you find**	**This hypothesis becomes**
Gastroesophageal reflux disease	Dysphagia	-2 -1 0 +1 +2
Gastroesophageal reflux disease	Worsening heartburn at bedtime or feeding	-2 -1 0 +1 +2
Myocardial ischemia	Electrocardiogram – normal	-2 -1 0 +1 +2
Malignant neoplasm of the esophagus	Dysphasia	-2 -1 0 +1 +2
Malignant neoplasm of the esophagus	Smoking	-2 -1 0 +1 +2

The panelists were asked to answer the test individually, and their answers were used to develop a scoring key. For each response, the score was the number of panel members who chose this response. Therefore, for every reference panel response to each question, a score of 0.1 was awarded, creating a maximum score of 1.0 for each question (**Table 2**).

The Microsoft Excel 2007 software was used to tabulate the data, and the statistical analysis was performed using the SPSS for Windows software, version 16.0. A value of 5% was used as the significance level ($P < 0.05$). The Kruskal-Wallis test was used to compare the variable of school year in relation to the score for each question. The overall Cronbach's alpha was calculated to evaluate the internal consistency among the questions.

RESULTS

Out of the total of 550 students (110 per school year from the first to fifth year), 159 participated in the study. There were 27/110 (24.5%) of the first-year students, 39/110 (35.5%) of the second-year students, 30/110 (27.3%) of the third-year students, 27/110 (24 5%) of the fourth-year students and 36/110 (32.7%) of the fifth-year students took the SCT, thus yielding the total of 159, or 28.9% of the students.

The reference panel shown in **Table 1** was used to grade the students' tests, according to year. In the reference panel, adding the highest score for each question and its items resulted in a total of 27 points. The first-year students obtained a mean of 13.39 points or 49.6% of the maximum score; the second-year students obtained a mean of 14.36 points or 53.2% of the maximum score; the third-year students obtained a mean of 16.32 points or 60.4% of the maximum score; the fourth-year students obtained a mean of 17.96 points or 66.5% of the maximum score, and the fifth-year students obtained a mean of 17.07 points or 63.2% of the maximum score.

The students were grouped as *pre-clinical*, i.e. those in the first and second years, who have no contact with patients; and *clinical*, i.e. those in the third, fourth and fifth years, who were already interacting with patients. Students in the pre-clinical phase obtained a mean of 13.94 points or 51.6% of the maximum score, and those in the clinical phase obtained a mean of 17.11 points or 63.4% of the maximum score.

Through completion of the Kruskal-Wallis test, which compared the means of the responses to each question and its items among students of all years, significant differences were only found in the following 20/50 items (40%): question 1 items 2, 3 and 5; question 2 items 1, 3, 4 and 5; question 3 items 1, 4 and 5; question 4 items 1 and 5; question 5 items 4 and 5; question 7 item 1; question 9 items 1, 3 and 5; and question 10 items 3 and 5.

The expert panel chose all the possible answers in question 3 item 3, question 5 item 2, question 6 item 4, question 9 item 2 and question 10 item 5. Additionally, the entire expert panel chose the same response in question 7 item 2.

The SCT instrument in this study had a reliability index (Cronbach's alpha) of 0.64.

DISCUSSION

In this study, 159/550 (28.9%) of the FM-UFG students took the test. This number corresponds to what has been found in other studies.[1,6,8-14]

In the present study, the SCT was applied to students at different stages of the medicine program at FM-UFG, from the pre-clinical phase (first and second years) to the clinical phase (third, fourth and fifth years). Students in the pre-clinical phase obtained a mean of 51.6% of the maximum score, and those in the clinical phase obtained a mean of 63.4% of the maximum score. There are few studies on the SCT with students in the pre-clinical phase.[10] Nonetheless, it is known that the SCT can be adapted to access knowledge at different stages of the medical curriculum.[15]

Comparing the mean scores of the students in the pre-clinical phase with those of the students in the clinical phase, an expected difference in student performance can be seen, with

Table 2. Reference panel answer spreadsheet

Value	Answers																								
	1/1	1/2	1/3	1/4	1/5	2/1	2/2	2/3	2/4	2/5	3/1	3/2	3/3	3/4	3/5	4/1	4/2	4/3	4/4	4/5	5/1	5/2	5/3	5/4	5/5
-2	0	0	0.5	0.1	0	0	0	0.7	0.9	0	0	0	0.1	0.3	0.6	0	0.1	0	0.1	0.4	0	0.2	0	0	0
-1	0	0	0.1	0.2	0	0	0.2	0.2	0	0	0	0	0.2	0.3	0.2	0	0	0	0.3	0.4	0	0.3	0.1	0	0.1
0	0.1	0	0.3	0.3	0.2	0.2	0	0.1	0.1	0	0.1	0	0.2	0.2	0.2	0	0.1	0.4	0.5	0.2	0.4	0.1	0.5	0	0
+1	0.5	0.2	0.1	0.2	0.4	0.3	0.7	0	0	0.4	0.2	0.1	0.4	0.2	0	0.3	0.7	0.6	0.1	0	0.4	0.3	0.3	0.4	0.2
+2	0.4	0.8	0	0	0.4	0.5	0.1	0	0	0.6	0.7	0.9	0.1	0	0	0.7	0.1	0	0	0	0.2	0.1	0.1	0.6	0.7
	6/1	**6/2**	**6/3**	**6/4**	**6/5**	**7/1**	**7/2**	**7/3**	**7/4**	**7/5**	**8/1**	**8/2**	**8/3**	**8/4**	**8/5**	**9/1**	**9/2**	**9/3**	**9/4**	**9/5**	**10/1**	**10/2**	**10/3**	**10/4**	**10/5**
-2	0	0	0	0.2	0	0.1	0	0.5	0	0.1	0.2	0.2	0.5	0.2	0.5	0.4	0.2	0.1	0	0	0	0	0	0	0.2
-1	0.1	0	0	0.1	0.2	0	0	0.2	0	0	0	0.3	0.2	0	0.2	0	0.1	0.1	0	0	0	0.1	0	0	0.1
0	0	0.2	0.1	0.4	0.3	0	0	0.3	0.2	0.5	0.2	0.4	0.2	0.5	0	0.5	0.1	0	0	0	0	0.1	0	0.2	0.4
+1	0.5	0.6	0.5	0.2	0.1	0.4	0	0	0.6	0.4	0.1	0.1	0.1	0.2	0.3	0.1	0.3	0.4	0.9	0.3	0.3	0.5	0.5	0.5	0.2
+2	0.4	0.2	0.4	0.1	0.4	0.5	1.0	0	0.2	0	0.5	0	0	0.1	0	0	0.3	0.4	0.1	0.7	0.7	0.3	0.5	0.3	0.1

Note: Each 0.1 corresponds to one professor's answer, thus totaling 1.0 for each item.

the senior students performing better. The SCT assumes that the individual examined interprets the data presented.[4] Therefore, it may be inferred that the more senior students will interpret the data in the scenarios presented and make decisions with a higher degree of agreement with the reference panel.[4,16]

The SCT was able to demonstrate that students in the preclinical and clinical phases had different levels of performance according to the degree of knowledge and maturity expected at each stage.[10,16]

Problems with SCT construction regarding several questions were identified in the present study. Only 40% of the items were able to differentiate between the students in the clinical and preclinical phases. In question 3 item 3, question 5 item 2, question 6 item 4, question 7 item 2, question 9 item 2 and question 10 item 5, there was very low discrimination. There were no significant differences among the five years of the program with these questions. Construction of an SCT with discriminative questions regarding clinical reasoning is not easily achieved.[8] In building the test, it is necessary to draw up questions with some variability in the responses offered by the reference panel, i.e. in which there is some disagreement among the panelists concerning certain items.[7,8] In the SCT, there is no right answer, and there may be many acceptable answers to each question. The score is dependent on the reference panel.[16]

In our test, in question 7 item 2, all the panelists chose the same answer (**Table 2**). Questions in which all the panelists provide the same answer do not differ from a multiple-choice test in their ability to assess students.[16]

In question 3 item 3, question 5 item 2, question 6 item 4, question 9 item 2 and question 10 item 5, the panel chose all possible answers (**Table 2**); thus, there was great variability. This type of question is too ambiguous and cannot be considered to represent good evaluative methodology.[7,16] Professionals and students in similar situations do not gather the same data and do not have the same thought patterns, which implies that differences over the interpretation of the data in SCT items represent valid differences of opinion. Decisions may be made in different ways, and those different ways will sometimes lead to the same decision. Reference panel members may think differently, but SCT panels should not include those with large differences in their clinical reasoning. The SCT scoring methodology would need to be reevaluated. This draws attention to the common occurrence in which a group of panelists believes that some of the information supports one hypothesis and another group believes the opposite. There may not be a correct answer for each SCT item, but a hypothesis should not be simultaneously the most and least likely answer. When panelists disagree in such a fundamental manner, it may indicate that there were problems in the construction of the question and that the right answer cannot be known.[4]

The SCT instrument in this study had a reliability index (Cronbach's alpha)[17] of 0.64, for an expected value of 0.70 - 0.90.[16] Some studies have reported similar results, in which this index is less than desirable.[8,9,18] This low reliability index may have occurred for several reasons, including the following:

- the problems cited regarding the construction of the questions;
- a reference panel of 10 professors, which is below the acceptable minimum;[7]
- applying an SCT based solely on diagnostic ability in internal medicine with volunteer professors from the FM-UFG Department of Clinical Medicine; these volunteers from various areas of knowledge were required to answer questions and items outside their area of specialized knowledge (for example, a panelist with expertise in cardiology was required to answer questions relating to nephrology), although all the panelists had knowledge of internal medicine; this type of panel may thus have caused some distortion in the reference panel answers; and
- using a five-point Likert scale.[2,4,6]

In smaller academic units with limited resources, it may be more efficient to replace the aggregate five-point scoring methodology[6] with consensus scoring methodology using a three-point scale ("unlikely", "neither likely nor unlikely" and "likely"), thereby possibly avoiding contradictory values in the scoring key.[4]

In medical education practice, all assessment instruments have limitations.[13] The SCT was developed within the context of the cognitive psychology approach known as script theory in order to assess how students and doctors organize their knowledge.[14] It is an instrument originally developed for medical education.[16] This is a test for which it is very difficult to construct questions; it requires a high degree of discrimination and therefore must involve a number of professors in different areas of medical knowledge in preparing the SCT. The scoring stage cannot be considered to be a simple process, because there is a need for both a reference panel with a minimum of 10 members[18] (who must have expertise in the areas of knowledge relating to the test) and for statistical analysis for the final student assessment. Thus, this is an assessment process with a high degree of difficulty in its preparation, implementation and scoring. It may be unfeasible to administer it in institutions with limited resources.

Regarding the limitations of this study, this test was the first SCT developed by our group. Due to local conditions, no pilot study (which might have overcome some of the difficulties) was conducted. The FM-UFG Department of Clinical Medicine has 42 professors, and 10 volunteered for the reference panel: this number was shown to be limited with regard to assessing various questions that were outside the panelists' area of expertise.

A traditional five-point Likert scale was selected for the SCT. However, we believe that these limitations do not invalidate the process developed and that the observations made in this study can help researchers and educators who plan to conduct the SCT.

CONCLUSION

The SCT was able to demonstrate that students in the pre-clinical and clinical phases had different levels of performance according to the degree of knowledge and maturity expected at each stage.

This instrument is very difficult to construct, apply and score. These factors may make the application of the SCT as an assessment method unfeasible in units with limited resources.

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Sources of funding: None
Conflict of interest: None

Date of first submission: January 13, 2015
Last received: May 25, 2015
Accepted: August 1, 2015

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Interaction of lipoprotein lipase polymorphisms with body mass index and birth weight to modulate lipid profiles in children and adolescents: the CASPIAN-III Study

Interação de polimorfismos da lipoproteína lipase com índice de massa corporal e peso ao nascer para modular o perfil lipídico em crianças e adolescentes: o estudo CASPIAN-III

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KEY WORDS:
Lipoprotein lipase.
Body mass index.
Birth weight.
Polymorphism, genetic.
Gene-environment interaction.

PALAVRAS-CHAVE:
Lipase lipoproteica.
Índice de massa corporal.
Peso ao nascer.
Polimorfismo genético.
Interação gene-ambiente.

ABSTRACT

CONTEXT AND OBJECTIVE: Interactions between body mass index (BMI), birth weight and risk parameters may contribute to diseases rather than the individual effects of each factor. However this hypothesis needs to be confirmed. This study aimed to determine to what extent variants of lipoprotein lipase (LPL) might interact with birth weight or body weight in determining the lipid profile concentrations in children and adolescents.

DESIGN AND SETTING: Substudy of the third survey of a national surveillance system (CASPIAN-III Study) in Iran.

METHODS: Whole blood samples (kept frozen at -70 °C) were randomly selected from 750 students aged 10-18 years. Real-time polymerase chain reaction (PCR) and high-resolution melt analysis were performed to assess S447X (rs328), HindIII (rs320) and D9N (rs1801177) polymorphisms.

RESULTS: The *AG/GG* genotype in D9N polymorphism was associated with higher LDL-C (low-density lipoprotein cholesterol) and lower HDL-C (high-density lipoprotein cholesterol) concentration. Significant interactions were found for D9N polymorphism and birth weight in association with plasma HDL-C concentration, and also for D9N polymorphism and BMI in association with plasma triglyceride (TG) and HDL-C levels. HindIII polymorphism had significant association with birth weight for HDL-C concentration, and with BMI for TG and HDL-C levels. Significant interactions were found for S447X polymorphism and BMI in association with plasma TG and HDL-C concentrations.

CONCLUSION: We found significant interactive effects from LPL polymorphisms and birth weight on HDL-C concentration, and also effects from LPL polymorphisms and BMI on TG and HDL-C concentrations.

RESUMO

CONTEXTO E OBJETIVO: Interações entre índice de massa corporal (IMC), peso ao nascer e parâmetros de risco podem contribuir para doenças, em vez de efeitos individuais de cada fator. No entanto, essa hipótese precisa de confirmação. Este estudo visou determinar o quanto variantes de lipoproteína lipase (LPL) podem interagir com peso de nascimento ou peso corporal na determinação das concentrações do perfil lipídico em crianças e adolescentes.

DESENHO E LOCAL: Sub-estudo da terceira pesquisa de sistema nacional de vigilância (Estudo CASPIAN-III) no Irã.

MÉTODOS: Foram selecionadas aleatoriamente amostras de sangue total (mantidas congeladas a -70 °C) de 750 estudantes com idades entre 10-18 anos. Reação de polimerase em cadeia (PCR) em tempo real e análise de fusão de alta resolução foram realizados para avaliar polimorfismo de S447X (rs328), HindIII (rs320) e D9N (rs1801177).

RESULTADOS: Genótipo AG/GG em polimorfismo D9N foi associado com concentração maior de LDL-C (colesterol do tipo lipoproteína de baixa densidade) e menor de HDL-C (colesterol do tipo lipoproteína de alta densidade). Interações significativas foram encontradas para polimorfismo D9N e peso ao nascer em associação com concentração plasmática de HDL-C, bem como para polimorfismo D9N e IMC em associação com níveis plasmáticos de triglicérides (TG) e HDL-C. Polimorfismo HindIII teve associação significativa com peso de nascimento para concentração de HDL-C, e com IMC para níveis de TG e HDL-C. Interações significativas foram encontradas para polimorfismo S447X e IMC em associação com concentrações plasmáticas de TG e HDL-C.

CONCLUSÃO: Encontramos efeitos interativos significativos de polimorfismo LPL e peso de nascimento sobre concentração de HDL-C, bem como efeitos de polimorfismos LPL e IMC sobre concentrações de TG e HDL-C.

INTRODUCTION

Adverse levels of serum lipoprotein cholesterols among children and adolescents are important risk factors for coronary artery and early stages of atherosclerosis. Serum lipid and lipoprotein levels in childhood are generally good predictors of their concentrations in young adulthood.[1] Elevated triglycerides (TG) and depressed HDL-C are the most common abnormalities of lipids and lipoproteins associated with obesity. This situation has been named atherogenic dyslipidemia.[2]

Some important genetic disorders increase the susceptibility to chronic diseases. Nonetheless, body weight, lifestyle habits and environmental factors, including the intrauterine environment, are important in determining the disease process.[3,4]

Several enzymes are involved in the metabolism of serum lipids. Lipoprotein lipase (LPL) has an important role in metabolism and transporting of lipids. It plays a major role in hydrolysis of chylomicrons and very low-density lipoproteins. The LPL gene has 10 exons and is located on chromosome 8p22. Recently, a number of more common single-nucleotide polymorphisms (SNPs) in the LPL gene have been described. These are related to lipid concentration, e.g. S447X (*C*-->*G* nucleotide 1595), HindIII (+495T > *G*) and D9N (*G*-->*A* nucleotide 280). It has been found that D9N has small deleterious effects on lipid profiles, whereas S447X has small beneficial effects on serum lipids in adults.[5]

Among perinatal characteristics, unfavorable birth weight and further growth trajectory are the most important factors relating to metabolic abnormalities.[6] The association between birth weight and the components of metabolic syndrome and other risk factors of cardiovascular disease (CVD) during childhood and adolescence remains controversial. Some studies have reported strong associations between low or high birth weight and the risk of CVD, while others have not found any association.[7,8] It has been suggested that some genes involved in metabolic processes may have different effects on people with different birth weights. Investigation on whether an adverse intrauterine environment and birth weight might alter the expression of genes relating to the lipid profile is clinically relevant.[9,10] Ruiz et al. hypothesized that some genes (APOE, APOC3 and PPARγ2 genes) might interact with birth weight to determine the blood lipid profile later in life. Their results suggested that the intrauterine environment would interact with the genetic background to determine plasma lipid profile levels in later life.[10]

Genetic factors are considered to be important determinants of plasma lipoprotein levels in adults. However, the role of genetics in determining plasma lipoproteins in children and adolescents is less clear. The increasing prevalence of dyslipidemia in children may be due to complex interactions between genetic and environmental factors. Studies have reported interactions between the LPL gene and lifestyle, in association with lipid profile concentrations in adults.[11,12] However, to the best of our knowledge, interactions with factors like birth weight have not been examined.

Some LPL genotypes have been found to have significant associations with changes to TG and HDL-C levels in obese subjects. These findings support the need for further studies to investigate the role of these polymorphisms in obesity.[13] The interaction between body mass index (BMI) and the LPL genotype may explain the deleterious role of obesity on lipid profile levels.[14]

Interactions between BMI, birth weight and risk parameters may contribute towards diseases, rather than the individual effects of each factor. However, this hypothesis needs to be confirmed. The link between BMI or birth weight and plasma lipid levels has been documented. Nonetheless, the interactions of single nucleotide polymorphisms (SNPs) and BMI or birth weight on plasma lipid levels are limited, particularly in children and adolescents.

OBJECTIVE

This study aimed to determine to what extent variants of LPL genes might interact with birth weight or body weight in determining the blood lipid profile concentration in children and adolescents.

METHODS

Study population

This study was conducted as a substudy of the "school-based nationwide health survey", which was the third survey of the school-based surveillance system named the Childhood and Adolescence Surveillance and PreventIon of Adult Noncommunicable disease (CASPIAN-III) Study.

The survey was conducted among 5570 students aged 10-18 years who were recruited by means of multistage random cluster sampling from urban and rural areas of 27 provincial counties in Iran. Students who had any chronic disease or who were taking medications were not included in this study. Complete data were obtained from 5528 students (2726 girls, 69.37% urban, mean age 14.7 ± 2.4 years) and were reported. Details of the data collection and sampling were published previously.[15] For the current study, we randomly selected 750 whole blood samples that had been kept frozen at -70 °C.

This survey was approved by ethics committees and other relevant national regulatory organizations. Written informed consent was obtained from parents and oral assent from the children and adolescents involved.

Physical examination and biochemical measurements

Weight and height were measured in accordance with standard protocols using calibrated instruments. Body mass index (BMI)

was calculated as the weight (kg) divided by the height squared (m^2). According to the World Health Organization (WHO) definition, normal weight was defined as a BMI Z-score between 1 and -2, wasting as a BMI Z-score between -2 and -3, risk of overweight as a BMI Z-score between 1 and 2, overweight as a BMI Z-score between 2 and 3, and obesity as a BMI Z-score of more than 3.[16] Birth weight was categorized as low birth weight (less than 2,500 g), normal (2,500-4,000 g) or high birth weight (more than 4,000 g).

To assess blood lipid levels, students were invited to go to the healthcare center nearest to their school. Fasting venous blood samples was taken. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured using auto-analyzers. HDL-C was measured after precipitation of non-HDL-C with dextran sulfate-magnesium chloride. The low-density lipoprotein cholesterol (LDL-C) levels in serum samples with TG < 400 mg/dl were calculated in accordance with the Friedewald equation. Total cholesterol (TC) was measured by means of an autoanalyzer.

The biochemical analyses were performed in the central provincial laboratory in each county. The methods used in these laboratories were in accordance with those of the National Reference laboratory, which is a WHO-collaborating center in Tehran.[15]

DNA extraction

DNA was extracted from peripheral blood using the QIAamp DNA blood mini-kit (Qiagen, Germany), in accordance with the manufacturer's protocol. Real-time polymerase chain reaction (PCR) and high-resolution melt (HRM) analyses were performed in the Corbett rotor-gene 6000 device (Corbett Research Pty Ltd, Sydney, Australia). Primers were designed using Beacon Designer 7.91 with the aim of flanking the genomic regions (Premier Biosoft International, USA) and were synthesized by TIB MOLBIOL (Germany).

Amplicons from all the genes were generated under the following conditions, using the Type-it HRM kit (Qiagen, Germany): one cycle at 95 °C for 15 minutes; 40 cycles at 95 °C for 15 seconds, 60 °C for 15 seconds and 72 °C for 15 seconds; and one cycle of 95 °C for 1 second, 72 °C for 90 seconds and a melt from 70 °C to 95 °C rising at 0.1 °C per second. The amplification mixture had a total volume of 25 µl and included 12.5 µl of HRM PCR master mix, 1.75 µl of 10 µM primer mix, 2 µl of genomic DNA as template and 8.25 µl of RNase-free water. For each genotype reaction, we included sequence-proven major and minor allele homozygote and heterozygote controls. The HRM analysis was performed using instrument software, which allowed clustering of the samples into groups based on difference plots that were obtained by analyzing the differences in melting curve shape between known controls and samples. The primer sequence used for LPL S447X rs328 was F: GCAGAAAGGAAAGGCACCTG, R: CAGGATGCC CAGTCAGCT; for LPL HindIII rs320, it was F: TCCAAGATA ATCTCAACCT, R: TAACAATAA- CAGCACACTATA; and for LPL D9N rs1801177, it was F: TCCAAGATAATCTCAACCT, R: GGAATGAGG- TGGCAAGTG.

Statistical analysis

The data were described by calculating the frequencies (percentages), means and standard deviation (SD). The differences between general characteristics based on LPL polymorphism levels were tested by means of the independent t test for quantitative variables and the chi-square test for qualitative variables. Separate analysis of covariance (ANCOVA) was done using each lipid profile as the dependent variable. Interactions between LPL gene variants and birth weight or BMI were assessed by using a cross-product term between genotypes and birth weight or BMI, on serum lipid levels that adjusted for age, sex, and physical activity. Statistical significance was evaluated through ANCOVA by using a custom model. Chi-square tests were used to assess Hardy-Weinberg expectations. The statistical analyses were performed using the SPSS statistical software package (version 20.0, SPSS Inc., Chicago, Illinois, USA). P-values of less than 0.05 were considered statistically significant.

RESULTS

The characteristics of the study participants according to genotypes are presented in **Table 1**. The P-values for Hardy-Weinberg expectations were 0.419 for D9N polymorphism, 0.105 for HindIII polymorphism and 0.06 for S447X polymorphism. The genotypic distribution of the three SNPs was in Hardy-Weinberg equilibrium (P > 0.05 for all). Overall, subjects with the variant allele (*AG* or *GG* genotype) and those with the *AA* genotype in D9N polymorphism did not differ significantly according to sex, age, fasting blood pressure (FBS), systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG or physical activity. LDL-C concentration and BMI were significantly higher among those with the *AG* or *GG* genotype than among those with the *AA* genotype. HDL-C concentration was significantly lower among those with the *AG* or *GG* genotype than among those with the *AA* genotype.

Compared with carriers of *GG* in HindIII polymorphism, those with *GT* or *TT* were slightly younger and had higher HDL-C and TC and lower TG and LDL-C concentrations and BMI (P < 0.05). No significant difference existed with regard to sex, FBS, SBP or DBP, between the *GG* and *GT/TT* genotype groups. Physical activity was significantly different between the groups. Those with the *GT/TT* genotype had higher percentages of physical activity in each category (mild, moderate or intense) than those with the *GG* genotype.

There were no significant differences in relating to age, FBS, DBP, SBP, TC, LDL-C, TG or BMI between the *CC* genotype and the *CG/GG* genotype in S447X polymorphism. Compared with carriers of *CC* in S447X polymorphism, those with the *CG/GG* genotype were slightly younger (14.23 ± 2.56 versus 14.75 ± 2.58; P = 0.03) and had higher HDL-C concentration (61.81 ± 21.85 versus 46.07 ± 20.69; P < 0.001). Physical activity was significantly different between the groups. Those with the *CC* genotype had higher percentages of physical activity in each category (mild, moderate or intense) than those with the *CG/GG* genotype.

The interaction effects between LPL genetic variants and birth weight on serum lipid levels after adjustment for age, sex, physical activity and BMI are presented in **Table 2**. In stratified analyses, the association between the LPL polymorphisms and plasma lipid profile concentrations varied according to the birth weight.

Significantly higher LDL-C and lower HDL-C concentration in relation to the *G* allele was confined to individuals with normal birth weight, in D9N polymorphism. For instance, among subjects with normal birth weight, plasma HDL-C concentration was significantly lower in those with the *AG/GG* genotype than in those with the *AA* genotype (35.82 ± 4.61 and 51.35 ± 1.11 mg/dl, respectively; P = 0.002). We observed a strong interaction between D9N polymorphism and birth weight in relation to HDL-C concentration.

Among those who had normal birth weight, the *T* allele in HindIII polymorphism was associated with significantly higher TC concentration (*GG* compared with *GT/TT*: 141.59 ± 2.82 and 151.52 ± 2.15 mg/dl, respectively; P = 0.003). This association was marginally significant among those with high birth weight (P = 0.053). Subjects with low birth weight and the *GT/TT* genotype had lower TG level (P = 0.01). This association was marginally significant among those with normal birth weight (P = 0.05). Only among normal birth weight subjects was the T allele associated with significantly depressed LDL-C concentration (P = 0.01). We observed a strong interaction between HindIII polymorphism and birth weight in relation to HDL-C concentration. Subjects with low, normal and high birth weight and the *GT/TT* genotype had higher HDL-C concentration than those with the *GG* genotype (P < 0.001).

Combinations of carrying the *G* allele in S447X polymorphism with normal or high birth weight were significantly associated with higher HDL-C concentration. No significant interaction was documented between birth weight and S447X polymorphism in relation to lipid profile concentrations.

Table 1. Characteristics of the study population across the lipoprotein lipase gene polymorphisms: the CASPIAN-III study

	D9N			HindIII			S447X		
	AA	AG + GG	P-value	GG	GT + TT	P-value	CC	CG + GG	P-value
% (n)	94.3 (707)	5.7 (43)		35.5 (266)	64.5 (484)		79.2 (594)	20.8 (156)	
Boy, % (n)	51.6 (365)	53.5 (23)	0.81	58.3 (155)	48.1 (233)	0.008	50.5 (300)	56.4 (88)	0.18
Girl, % (n)	48.4 (342)	46.5 (20)		41.7 (111)	51.9 (251)		49.5 (294)	43.6 (68)	
Age	14.65 ± 2.6	14.53 ± 2.3	0.77	14.9 ± 2.5	14.5 ± 2.6	0.04	14.75 ± 2.58	14.23 ± 2.56	0.03
FBS	86.69 ± 13.46	83.52 ± 11.58	0.13	85.63 ± 13.78	86.99 ± 13.13	0.19	86.25 ± 13.38	87.47 ± 13.35	0.31
SBP	102.89 ± 13.55	101.91 ± 10.7	0.64	103.88 ± 13.31	102.23 ± 13.4	0.12	102.96 ± 13.54	102.29 ± 12.76	0.60
DBP	65.99 ± 10.55	66.53 ± 11.7	0.74	66.26 ± 11.39	65.89 ± 10.17	0.65	66.29 ± 10.75	65.01 ± 10.07	0.19
TC	147.93 ± 34.45	147.16 ± 34.61	0.88	143.08 ± 32.25	150.5 ± 35.35	0.005	146.71 ± 35.04	152.32 ± 31.84	0.07
LDL	81.47 ± 32.14	95.96 ± 35.38	0.005	88.64 ± 30.96	78.81 ± 32.82	< 0.001	83.40 ± 32.61	78.17 ± 31.77	0.08
HDL	50.32 ± 22.01	33.26 ± 10.34	< 0.001	34.54 ± 10.6	57.48 ± 22.21	< 0.001	46.07 ± 20.69	61.81 ± 21.85	< 0.001
TG	93.37 ± 43.72	87.09 ± 33.93	0.36	100.49 ± 50.17	88.88 ± 38.29	0.001	94.58 ± 45.57	87.02 ± 32.12	0.06
Physical activity % (n)									
Mild	35.2 (224)	37.8 (14)		42.7 (99)	31.5 (139)		37.3 (199)	28.1 (39)	
Moderate	33.6 (214)	27.0 (10)	0.70	31.5 (73)	34.2 (151)	0.01	33.9 (181)	30.9 (43)	0.02
Intense	31.1 (198)	35.1 (13)		25.9 (60)	34.2 (151)		28.8 (154)	41.0 (57)	
BMI	19.02 ± 3.93	20.92 ± 5.67	0.003	19.76 ± 4.34	18.79 ± 3.88	0.002	19.21 ± 4.04	18.84 ± 4.21	0.31
BMI % (n)									
Underweight	20.4 (141)	16.3 (7)		18.1 (47)	21.3 (101)		20.0 (116)	20.8 (32)	
Normal	64.8 (448)	48.8 (21)	0.002	61.8 (160)	65.1 (309)	0.06	63.3 (367)	66.2 (102)	0.53
Overweight + obese	14.8 (102)	34.9 (15)		20.1 (52)	13.7 (65)		16.7 (97)	13 (20)	
Birth weight % (n)									
< 2500 g	13.1 (86)	26.3 (10)		14.6 (36)	13.4 (60)		14.8 (81)	10.3 (15)	
2500 – 4000 g	78.6 (515)	63.2 (24)	0.054	76.8 (189)	78.3 (350)	0.89	77.1 (422)	80.1 (117)	0.33
> 4000 g	8.2 (54)	10.5 (4)		8.5 (21)	8.3 (37)		8.0 (44)	9.6 (14)	

FBS = fasting blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglyceride; BMI = body mass index.

The interaction effects between LPL genetic variants and BMI on serum lipid level, after adjustment for age, sex, physical activity and birth weight, are presented in **Table 3**. We observed interaction between D9N polymorphism and BMI in relation to TG and HDL-C concentrations ($P < 0.001$ and $P = 0.04$, respectively). Underweight and normal-weight individuals with the *AG/GG* genotype had lower HDL-C level than those with the *AA* genotype ($P = 0.01$).

Table 2. Interactions between lipoprotein lipase gene variants and birth weight, in relation to serum lipid levels in Iranian children and adolescents: the CASPIAN-III study

	D9N				HindIII				S447X			
	AA	AG + GG	P-value	P int	GG	GT + TT	P-value	P int	CC	CG + GG	P-value	P int
TC												
BW < 2500 (n = 96)	148.92 ± 4.05	145.09 ± 12.50	0.44		152.08 ± 6.03	146.52 ± 4.81	0.31		148.11 ± 4.09	151.85 ± 10.29	0.5	
BW = 2500-4000 (n = 537)	147.87 ± 1.88	149.76 ± 7.73	0.76	0.87	141.59 ± 2.82	151.52 ± 2.15	0.003	0.12	146.89 ± 2.01	152.06 ± 3.53	0.16	0.9
BW > 4000 (n = 58)	153.33 ± 5.19	150.59 ± 17.66	0.89		136.93 ± 8.27	161.74 ± 5.99	0.053		152.51 ± 5.74	155.14 ± 9.49	0.89	
P-value	0.56	0.96			0.16	0.15			0.60	0.99		
TG												
BW < 2500 (n = 94)	102.45 ± 4.89	85.37 ± 14.91	0.06		111.56 ± 7.25	93.37 ± 5.89	0.01		100.37 ± 4.95	101.99 ± 12.31	0.46	
BW = 2500-4000 (n = 533)	97.75 ± 2.24	79.93 ± 9.23	0.08	0.71	101.53 ± 3.39	93.97 ± 2.59	0.05	0.51	98.42 ± 2.40	90.46 ± 4.24	0.07	0.73
BW > 4000 (n = 58)	91.65 ± 6.19	83.09 ± 21.07	0.41		101.55 ± 9.95	84.66 ± 7.21	0.07		92.62 ± 6.86	84.87 ± 11.35	0.5	
P-value	0.39	0.8			0.43	0.43			0.66	0.45		
LDL-C												
BW < 2500 (n = 94)	87.17 ± 3.77	88.32 ± 11.48	0.83		95.64 ± 5.59	82.14 ± 4.55	0.06		87.67 ± 3.83	86.04 ± 9.51	0.84	
BW = 2500-4000 (n = 527)	80.01 ± 1.74	96.93 ± 7.10	0.02	0.27	85.91 ± 2.62	78.32 ± 2.02	0.01	0.18	81.82 ± 1.86	77.91 ± 3.32	0.24	0.38
BW > 4000 (n = 57)	85.14 ± 4.83	109.83 ± 16.22	0.34		84.62 ± 7.67	88.57 ± 5.65	0.81		88.99 ± 5.31	82.49 ± 9.11	0.1	
P-value	0.13	0.88			0.28	0.19			0.18	0.70		
HDL-C												
BW < 2500 (n = 96)	42.83 ± 2.41	40.86 ± 7.44	0.54		30.86 ± 3.19	50.02 ± 2.54	< 0.001		41.11 ± 2.38	52.39 ± 5.98	0.12	
BW = 2500-4000 (n = 539)	51.35 ± 1.11	35.82 ± 4.61	0.002	0.009	36.38 ± 1.49	58.27 ± 1.14	< 0.001	0.006	47.39 ± 1.16	61.86 ± 2.05	< 0.001	0.08
BW > 4000 (n = 58)	52.73 ± 3.09	24.09 ± 10.51	0.04		30.66 ± 4.38	61.11 ± 3.17	< 0.001		46.63 ± 3.34	61.03 ± 5.52	0.03	
P-value	0.003	0.19			0.005	0.03			0.04	0.38		

P_{int} = P interaction; TC = total cholesterol; BW = birth weight; TG = triglyceride; LDL-C = low-density lipoprotein; HDL-C = high-density lipoprotein. Data are mean ± Standard Error (SE). Model adjusted for age, sex, physical activity and BMI.

Table 3. Interactions between lipoprotein lipase gene variants and body mass index, in relation to serum lipid levels in Iranian children and adolescents: the CASPIAN-III study

	D9N				HINDIII				S447X			
	AA	AG + GG	P-value	P int	GG	GT + TT	P-value	P int	CC	CG + GG	P-value	P int
TC												
Underweight (n = 148)	3.71 ± 147.91	15.80 ± 143.48	0.66		5.78 ± 143.05	4.25 ± 150.26	0.19		4.03 ± 147.92	6.96 ± 146.79	0.65	
Normal (n = 468)	2.32 ± 150.16	9.43 ± 153.09	0.67	0.92	3.34 ± 143.56	2.57 ± 153.61	0.008	0.87	2.46 ± 148.22	4.00 ± 157.10	0.06	0.42
Overweight + obesity (n = 116)	4.17 ± 151.86	9.51 ± 150.31	0.97		5.51 ± 147.91	4.96 ± 154.32	0.51		4.12 ± 152.65	9.06 ± 145.57	0.64	
P-value	0.73	0.72			0.65	0.75			0.59	0.29		
TG												
Underweight (n = 146)	4.42 ± 83.01	18.84 ± 75.56	0.63		6.93 ± 87.51	5.09 ± 79.72	0.27		4.81 ± 82.83	8.32 ± 78.95	0.73	
Normal (n = 461)	2.79 ± 90.24	11.25 ± 90.79	0.43	< 0.001	4.01 ± 98.49	3.10 ± 85.12	0.002	< 0.001	2.96 ± 89.94	4.80 ± 86.67	0.47	< 0.001
Overweight + obesity (n = 116)	4.94 ± 119.96	11.34 ± 92.90	0.09		6.53 ± 115.85	5.94 ± 116.42	0.82		4.90 ± 120.48	10.83 ± 89.32	0.11	
P-value	< 0.001	0.28			0.02	< 0.001			< 0.001	0.68		
LDL-C												
Underweight (n = 142)	3.48 ± 81.73	14.53 ± 97.96	0.66		5.36 ± 89.47	4.04 ± 78.92	0.16		3.77 ± 83.82	6.71 ± 78.01	0.15	
Normal (n = 460)	2.15 ± 84.11	8.67 ± 98.90	0.07	0.91	3.11 ± 89.19	2.39 ± 82.66	0.04	0.35	2.29 ± 85.41	3.72 ± 82.68	0.39	0.76
Overweight + obesity (n = 115)	3.86 ± 86.35	8.75 ± 99.05	0.17		5.05 ± 92.71	4.67 ± 84.93	0.27		3.83 ± 89.43	8.65 ± 81.90	0.41	
P-value	0.59	0.80			0.77	0.61			0.52	0.87		
HDL-C												
Underweight (n = 148)	2.21 ± 52.55	9.43 ± 28.45	0.01		3.05 ± 35.58	2.24 ± 59.63	< 0.001		2.35 ± 48.21	4.06 ± 62.93	0.002	
Normal (n = 469)	1.38 ± 50.32	5.63 ± 36.54	0.01	0.04	1.77 ± 34.41	1.35 ± 57.21	< 0.001	0.02	1.44 ± 46.55	2.33 ± 60.75	<0.001	0.03
Overweight + obesity (n = 117)	2.47 ± 43.77	5.67 ± 33.67	0.06		2.88 ± 31.91	2.62 ± 49.78	< 0.001		2.39 ± 40.17	5.29 ± 53.23	0.004	
P-value	0.01	0.66			0.16	0.03			0.01	0.31		

P_{int} = P interaction; TC = total cholesterol; TG = triglyceride, LDL-C = low-density lipoprotein; HDL-C = high-density lipoprotein. Data are mean ± Standard Error (SE). Model adjusted for age, sex, physical activity and birth weight.

In joint analysis, combinations of carrying the *T* allele (*GT/TT* genotype) with normal weight were significantly associated with higher TC and HDL-C levels, and also with lower TG and LDL-C concentrations, than those of subjects with the *GG* genotype in HindIII polymorphism. Among underweight and overweight/obese subjects, carrying the *T* allele was associated with higher HDL-C concentration than that of subjects with the *GG* genotype ($P < 0.001$). Moreover, interaction between HindIII polymorphism and BMI was found for TG and HDL-C concentrations ($P < 0.001$ and $P = 0.02$, respectively).

Underweight, normal weight and overweight/obesity in subjects with the *G* allele were associated with elevated HDL-C concentrations in S447X polymorphism. Interaction between S447X polymorphism and BMI existed in relation to TG and HDL-C concentrations ($P < 0.001$ and $P = 0.03$, respectively).

Linear regression models after adjustment for confounders showed that D9N polymorphism was significantly positively related to LDL-C in the normal birth weight group (â ± standard error (SE) = 18.51 ± 6.57; P-value = 0.005), and significantly negatively related to HDL-C in the normal and > 4000 g birth weight groups (â ± SE = -17.68 ± 4.52; P-value = < 0.001; and â ± SE = -26.53 ± 5.02; P-value = 0.03, respectively). However, D9N polymorphism was not significantly associated with total cholesterol and TG in any of the birth weight groups. HindIII polymorphism was positively related to HDL-C and negatively related to TG, in all the birth weight groups. In addition, HindIII had a beneficial effect on LDL-C (â ± SE = -9.98 ± 2.85; P-value = 0.001) in the normal birth weight group. Thus, HindIII polymorphism may improve lipid profiles. S44X polymorphism was significantly positively associated with HDL-C alone, in all the birth weight groups (birth weight < 2500 g: â ± SE = 11.36 ± 4.34; P-value = 0.003; birth weight 2500-4000 g: â ± SE =15.31 ± 2.19; P-value = 0.001; and birth weight > 4000 g: â ± SE = 16.89 ± 3.02; P-value = 0.01). In different BMI categories, a significant adverse association was found between D9N polymorphism and HDL-C (underweight: â ± SE = -19.49 ± 8.44; P-value = 0.02; normal: â ± SE = -17.44 ± 4.88; P-value = < 0.001; and overweight + obese: â ± SE = -11.46 ± 5.22; P-value = 0.02). A significant association was found for HindIII and S447X polymorphisms in relation to elevated HDL-C, in all BMI categories. In addition, HindIII polymorphism had a beneficial effect on other lipid profiles in the normal BMI category (these data were not shown).

DISCUSSION

We showed that the *AG/GG* genotype in D9N polymorphism is associated with higher LDL-C and lower HDL-C concentrations. However, these associations were observed only among individuals who had normal birth weight, and among underweight and normal-weight subjects according to BMI. Significant interactions were found for D9N polymorphism and birth weight in association with plasma HDL-C concentrations, and also for D9N polymorphism and BMI in association with plasma TG and HDL-C levels. Our data suggest that the effect of LPL polymorphisms on the lipid profile is modulated by either birth weight or BMI.

One case-control study in Australia showed that D9N polymorphism did not significantly influence HDL-C or TG.[17] Other studies showed that D9N polymorphism had an adverse effect on serum lipids, and increased the risk of CVD.[18,19] It is possible that D9N polymorphism leads to deficiency of LPL secretion.[17]

The importance of the gene/environment interaction has been discussed in relating to human disease processes and disease prevention. Regulation of lipid profile concentrations is a complicated and poorly understood process that may depend on interactions of both environmental and genetic factors. Researchers have hypothesized that the interactions between some genetic polymorphisms and environmental factors may be related to serum lipid levels.[20,21] Several studies have investigated the influence of weight or birth weight on plasma lipid levels.[22] LPL polymorphisms also affect lipid concentrations.[23] However, the interaction between BMI or birth weight and the polymorphisms of LPL, on serum lipid levels, is not well known, particularly among children and adolescents. It is noteworthy to mention that in the current study, HindIII polymorphism had a significant association with birth weight, in relation to HDL-C concentration, and with BMI in relation to TG and HDL-C levels. The *GT/TT* genotype in HindIII polymorphism is associated with higher TC and HDL-C and lower TG and LDL-C concentrations.

HindIII polymorphism is a thymine to guanine base transition at position +495 in intron 8 and is one of the most common polymorphisms in the LPL gene.[24] The association between HindIII polymorphism and TG is more controversial. While some studies have shown significant associations between HindIII polymorphism and hypertriglyceridemia,[25,26] these findings have not been confirmed by others.[27,28] However, most studies have proposed that this polymorphism is a modulator of plasma lipid levels.[29,30] The mechanism of its effect on plasma lipid levels remains to be determined.[24]

In this study, plasma HDL-C levels were significantly higher in individuals with the *G* allele (*CG* or *GG* genotype) than in those with the *CC* genotype in S447X polymorphism. Significant interactions were found for S447X polymorphism and BMI in association with plasma TG and HDL-C concentrations.

Nettleton et al.[31] showed that white and African-American adults with the *CG/GG* genotype had higher HDL-C and lower TG concentrations than their counterparts. This profile is generally associated with reduced risk of CVD. Likewise, a case-control study in India confirmed that in CVD patients, Ser447X polymorphism was associated with decreased TG levels and that

this effect was possibly due to increased LPL activity.[30] A meta-analysis on previous studies among adults showed that S447X polymorphism decreased TG and increased HDL-C, and therefore decreased the CVD risk.[32]

The key role of LPL is in postprandial lipid metabolism. However, it is also involved in metabolism of fasting lipid. S447X polymorphism affects postprandial lipemia, and this may be a mechanism for its effects on TG and HDL-C concentrations.[31]

However, the mechanism for the effects of this polymorphism on serum lipid metabolism remains obscure. One study suggested that S447X polymorphism might alter LPL translation,[33] but its mechanism is unclear.[32]

A previous study speculated that the gene encoding LPL played an important role in dyslipidemia in an Asian population.[13] LPL has a central role in lipid metabolism. There is a clear relationship between LPL activity and lipid concentrations. Insulin is a major regulator of LPL activity. Since insulin levels and activity are related to body weight, it can be hypothesized that LPL activity is affected by obesity. It has been shown that LPL polymorphisms affect plasma lipid concentration to a greater or lesser degree in individuals with different BMI levels.[13,14]

To the best of our knowledge, no previous study has reported on interactions between LPL polymorphisms and birth weight or between LPL polymorphisms and BMI interactions, in relation to serum lipid concentrations in children and adolescents. It is plausible that interactions between birth weight or BMI and the LPL polymorphisms in association with serum lipid concentrations might occur through their effects on LPL activity.

Studies have shown that there are low TG concentrations in overweight and obese individuals who carry the *T* allele, which in turn might be due to increased LPL activity. Furthermore, overweight and obese individuals with the *GG* genotype have been found to have higher serum TG levels than their non-obese counterparts.[11] A cross-sectional study showed that, among obese subjects, carrying the S447X allele alone was associated with lower TG concentrations. Thus, TG levels were modified significantly by interactions between LPL polymorphism and BMI in adults.[34] We also observed significant interactions between LPL polymorphisms and BMI in association with lipid profile in children and adolescents.

On the other hand, another study that investigated interactions between obesity and the S447X polymorphism showed that subjects with S447X polymorphism and normal BMI had significantly lower TG concentration. However, no significant difference was documented for those with excess weight.[35] In another study, the HindIII polymorphism was strongly correlated with hypertriglyceridemia in obese subjects.[36]

The responsiveness of LPL to glucose or insulin stimuli is delayed in the adipose tissue of obese subjects. Therefore, it is supposed that obesity might lead to a condition that may increase genetic susceptibility to hyperlipidemia and diabetes.[37]

It has been found that birth weight might affect cardiovascular events and the components of metabolic syndrome.[38,39] Some researchers have proposed that this relationship is genetically mediated.[40] Among adult men, higher birth weight has been correlated with decreased TC levels.[41] Several studies have reported a U-shaped association between birth weight and cardiovascular risk factors in children and adolescents.[42,43] Numerous cohort and experimental studies on animals have confirmed that fetal programming of adult diseases exists, and have suggested that undernutrition during fetal life and low birth weight can lead to future disease.[44,45] Reduced fetal growth may have adverse consequences on liver growth. Poor liver growth may cause disorders of blood lipid metabolism.[10]

However, the underlying molecular and genetic mechanisms of the association of birth weight with disease in later life are not clearly understood.[44] We observed significant interactions between LPL polymorphisms and BMI in association with some lipid profiles in children and adolescents. No previous data from children are available for comparison.

Interactions between BMI and LPL polymorphisms or between birth weight and LPL polymorphisms may explain how subjects with a certain genotype fail to maintain homeostasis and ideal levels of plasma lipids only after the environmental challenge of increasing obesity. Our results showed that the differences in the lipid profile levels of underweight, normal weight and overweight/obese subjects or between birth weight categories might be partly because of different interactions between some SNPs and BMI or birth weight in the population studied.

According to the linear regression model, our findings suggest that there is a beneficial association between HindIII or S447X polymorphism and lipid profile, particularly with regard to HDL-C levels, in all categories of birth weight or BMI. We can conclude that these two polymorphisms may improve lipid profiles in children and adolescents. However, D9N had undesirable effect on lipid profiles.

Study limitations and strengths: The main limitation of this study is the cross-sectional nature of the associations. Other possible study limitations include the small sample size in some subgroups, particularly in the groups of individuals with birth weight > 4000 g and with the *AG/GG* genotype for D9N. The strengths of this study are its novelty in the pediatric age group, and its inclusion of a relatively large number of population-based samples.

CONCLUSION

We observed that children and adolescents with the HINDIII and S447X alleles had better serum lipid profiles than those of non-carriers. We found significant interactive effects between LPL

polymorphism and birth weight, in relation to HDL-C concentrations, and also significant effects between LPL polymorphism and BMI in relation to TG and HDL-C concentrations. The clinical significance of these associations needs to be confirmed in future longitudinal studies.

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Sources of funding: This study was funded by Iran National Science Foundation (Grant No. 89000784) and Isfahan University of Medical Sciences, Isfahan, Iran. The project was approved by Isfahan University of Medical Sciences, Isfahan, Iran
Conflict of interests: None

Date of first submission: April 25, 2015
Last received: August 20, 2015
Accepted: August 26, 2015

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DOI: 10.1590/1516-3180.2015.01332210

Mistreatment in an academic setting and medical students' perceptions about their course in São Paulo, Brazil: a cross-sectional study

Maus-tratos em um ambiente acadêmico e percepção sobre o curso entre estudantes de medicina em São Paulo, Brasil: um estudo transversal

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KEY WORDS:
Human rights abuses.
Aggression.
Social behavior.
Bullying.
Students, medical.
Education, medical.

PALAVRAS-CHAVE:
Violações dos direitos humanos.
Agressão.
Comportamento social.
Bullying.
Estudantes de medicina.
Educação médica.

ABSTRACT

CONTEXT AND OBJECTIVE: High prevalence of mistreatment among medical students has been described in the worldwide literature since the 1980s. However, studies addressing the severity and recurrence of victimization and its effects on students' perceptions of their medical course are scarce. This study had the aim of estimating the prevalence of exposure to mistreatment that was considered to be severe and recurrent and its association with medical students' perceptions about their medical course.

METHODS: A cross-sectional study was conducted in a medical school in São Paulo, Brazil. Three hundred and seventeen students from the first to the sixth year answered the online questionnaire.

RESULTS: High prevalence of mistreatment during the course was found. Two thirds of the students considered the episodes to be severe, and around one third reported experiencing recurrent victimization. Occurences of mistreatment that the students considered to be severe were correlated with feeling overloaded and wanting to abandon the medical course.

CONCLUSIONS: Occurrences of mistreatment within the academic environment are frequent in Brazil. The results suggest that mistreatment that was considered to be severe might negatively affect students' perceptions about their course.

RESUMO

CONTEXTO E OBJETIVO: Altas prevalências de maus-tratos entre estudantes de medicina vêm sendo descritas na literatura internacional desde a década de 1980. Estudos sobre a gravidade e recorrência da vitimização e seus efeitos na percepção dos alunos sobre o curso médico são escassos. Este estudo tem por objetivo estimar a prevalência de exposição a maus-tratos considerados graves e recorrentes e sua associação com a percepção dos estudantes de medicina sobre o curso médico.

MÉTODOS: Estudo transversal realizado em uma escola médica em São Paulo, Brasil. Trezentos e dezessete estudantes do primeiro ao sexto ano responderam ao questionário *online*.

RESULTADOS: Foram encontradas altas prevalências de maus-tratos durante o curso. Dois terços dos estudantes consideraram os maus-tratos graves e cerca de um terço referiu vitimização recorrente. A ocorrência de maus-tratos considerados graves pelos estudantes esteve associada a sentimento de sobrecarga e desejo de abandonar o curso médico.

CONCLUSÃO: A ocorrência de maus-tratos no ambiente acadêmico é frequente no Brasil. Os resultados sugerem que os maus-tratos percebidos como graves podem afetar negativamente a percepção dos estudantes sobre o curso.

INTRODUCTION

The high prevalence of mistreatment towards medical students has been identified as an important issue in medical education since the late 1980s and early 1990s. Since that time, studies conducted in different countries[1-13] have corroborated the high prevalence of different forms of aggression within medical education, thus giving support to the idea that these abusive situations reflect a strongly hierarchical medical culture.[14]

Even though this problem was first described in the late 1980s, the prevalence of abuse, harassment and mistreatment among medical students remains high in different countries. Considering only studies that focused on the concept of bullying and thus limited their analysis to situations that were repetitive and persistent, the prevalence has ranged from 19.7% in Colombia[8] to 52% in Pakistan.[6] Studies that used broader concepts, including harassment, belittlement, discrimination and abuse not limited to persistent and chronic situations, have found higher prevalence rates: 18.9%,[4] approximately 40%[2,5] and more than 90%.[1,3,12]

Studies conducted in the US by Sheehan et al.[15] and Rosenberg[16] brought to light not only the high prevalence of mistreatment but also its negative consequences for academic achievement and later professional conduct. Although the effects on students' mental health, wellbeing and perceptions about medical education and academic achievements are well known,[5,7,12,16-20] studies addressing the perceived severity and recurrence of mistreatment and the association with students' perceptions about their medical course are scarce. Most of the studies have been conducted in the US, and no data are available for Brazil.

Medical courses in Brazil have a minimum duration of six years. Basic science disciplines are usually provided in the first two years, and disciplines focusing on training for general medical practice and medical specialties in the third and fourth years. Internship, i.e. the mandatory clinical training period, takes place in the last two years, with activities within healthcare services. In Brazil, students start medical education earlier; medical education may be the first undergraduate course and may immediately follow the secondary school cycle. Thus, medical education can start as early as the ages of 17 or 18 years, with no previous university or college experience. Exposure to different forms of mistreatment within the academic environment at such an early age can have an even more pronounced negative impact, especially in cases that are recurrent or that students consider important. Our hypothesis was that mistreatment that was perceived as severe or recurrent was associated with a negative impact on the way in which students perceive medical education and their academic achievements.

OBJECTIVE

Our aim was to estimate the prevalence of mistreatment that was perceived as severe and recurrent among medical students and to investigate the association with medical students' perceptions about their medical course.

METHODS

Study design and participants

The QUARA project (Quality of Relationships in the Academic Environment) was a cross-sectional study undertaken in a Brazilian public medical school in the city of São Paulo from September to December 2013 that evaluated medical students with regard to the following: mistreatment, socioeconomic characteristics, aspects of the medical course, mental health problems before starting the medical course, lifestyle habits, depression, burnout, social support, quality of life, stressful life events and professional conduct.

All the medical students who were formally registered in 2013 in the same medical school (n = 1,072) were invited to participate in the study, through an initial email containing a link to an informed consent statement and the full questionnaire. Weekly reminders followed the initial email invitation. Additional awareness-raising initiatives included face-to-face reminders during lectures by a student reference group, Facebook posts and distribution of flyers.

Procedures

To facilitate data collection, an online questionnaire was created using REDCap (Research Electronic Data Capture).[21] A pilot study was conducted (n = 10) before the beginning of data collection in order to test the procedures and identify unclear questions. Authorization for translation and use of the questionnaire Perception of Medical Students on their Learning Environment[4] was obtained from its author.

The ethics committee of the Medical School of the University of São Paulo (FMUSP) approved this research. Privacy and confidentiality were guaranteed for all participants, and all students signed an informed consent form before participation (Ref 345.993, July 31, 2013).

Measurements

Mistreatment

The questions about mistreatment were derived from the questionnaire Perception of Medical Students on their Learning Environment[4] and were translated by two independent translators following three steps: 1) translation into Portuguese, 2) back-translation and 3) group discussion to establish the final version. The validity of the questionnaire was not assessed.

This questionnaire addresses the following types of mistreatment by different perpetrators (professors, students, residents,

preceptors/supervisors, attending physicians, nurses, other healthcare professionals, patients or their families and others): shouting/yelling, depreciation/humiliation, task assignment with punitive purposes, derogatory comments about the career, racial/religious discrimination, threat of injury, threat of physical harm, sexual harassment and discrimination and physical violence (slap, push, kick or hit). The responses are 1 (never), 2 (rarely; 1-2 times), 3 (sometimes; 3-4 times) and 4 (often; 5 times or more). For this paper, we took exposure to any type of mistreatment to be a binary variable (0: never/rarely/sometimes; or 1: often, 5 times or more). If a student answered "five times or more" for at least one type of mistreatment, this was considered to be recurrent mistreatment.

An additional question assesses how much each of the mistreatments bothered the student. The responses include the following options: 0 (does not apply; was not a victim), 1 (not at all), 2 (a little) and 3 (a lot). For the purpose of our analysis, a binary variable expressing the importance attributed by the students to the mistreatment suffered was recoded as 0 (was not a victim/not at all, a little) or 1 (a lot). If a student answered "bothered a lot" for at least one type of mistreatment, this was considered to be mistreatment perceived as severe by the student. This variable expresses students' perception, and does not take any external parameter of gravity into consideration.

Perception of medical course

Four questions addressed the students' perceptions concerning their medical course: 1) Are you satisfied with your professional choice? a) yes or b) no/I don't know; 2) Have you ever considered dropping out of this course? a) no or b) yes, I did in the past/yes, I still think about it; 3) Do you think your academic achievement is excellent, good, fair or poor? a) excellent/good or b) fair/poor; 4) Do you feel overloaded by the activities you perform as part of your course? a) yes or b) no.

Statistical analysis

All the data analyses were performed using Stata 13.0. The prevalence of exposure to recurrent mistreatment or mistreatment perceived as severe was calculated. The associations that recurrent mistreatment and mistreatment perceived as severe presented in relation to the perception of overload, dissatisfaction with the medical course, willingness to drop out and perception of poor academic achievement were calculated through Poisson regression analysis after adjusting for sex, age, skin color, whether student was admitted to course through the social inclusion policy and school cycle. Poisson regression was the statistical method chosen because this method enables calculation of prevalence ratios and gives better estimates when dealing with high-prevalence outcomes.

The prevalence and prevalence ratios were estimated after ranking adjustments and post-stratification weighting by considering the distribution of all the students in the medical school according to gender and class for the whole sample and according to school cycle. Confidence intervals (95%) were calculated for all point estimates. The chi-square test was used to test for linear trend according to school cycle.

RESULTS

Out of the 1,072 students invited, 338 (31.5%) agreed to participate in the survey. Of these, 317 students completed the interview. Approximately 50% of the respondents were female. Most participants were 23 years old or older, and the mean age was 22.4 years (standard deviation, SD = 2.8). White was the skin color most reported. Nearly 45% of the sample was in the basic science years of medical education, and only 22% were in the clinical cycle (internship) (**Table 1**).

The overall prevalence of mistreatment among medical students during their training years was extremely high (92.3%) (**Table 2**). Recurrent mistreatment was reported by 30.1% of the participants, and most students (64.2%) reported having been exposed to mistreatment that they perceived as severe. The exposure to overall, recurrent and severe mistreatment increased over the duration of the course, with higher prevalence during the clinical years. A significant linear trend was found for severe mistreatment. This probably expresses the cumulative dimension of our measurement, since we asked about occurrences of mistreatment over the duration of the course.

A negative perception of the medical course was common in our sample: 80% of the students felt overloaded, nearly 20%

Table 1. Characteristics of the participants (n = 317). São Paulo, Brazil, 2013

	n	%
Sex		
Male	156	49.3
Female	161	50.7
Skin color		
Caucasian	238	75.1
Other	79	24.9
Age (years)		
17 to 23	227	71.6
Over 23	90	28.4
Student was admitted to course through social inclusion policy for access to university		
Yes	69	21.7
No	248	78.3
School cycle		
Basic (years 1 and 2)	142	44.7
Preclinical (years 3 and 4)	104	32.8
Clinical (years 5 and 6)	71	22.4

reported feeling dissatisfied and nearly 35% had considered dropping out of their medical course (**Table 2**). Basic year students presented negative perceptions about the course more frequently. Clinical year students reported having considered dropping out of the course more frequently. No linear trend was found.

Being exposed to recurrent mistreatment (five times or more) was not associated with any of the indicators of negative perception about the course (**Table 3**). However, being exposed to mistreatment that was perceived as severe was associated with higher prevalence of perceived overload and considering dropping out of the course, in both the crude and the adjusted models. Students who were exposed to mistreatment that they perceived as severe felt more overloaded (prevalence ratio, PR = 1.17; 95% confidence interval, CI: 1.02; 1.36) and had considered dropping out of the course more frequently than those not exposed (PR = 2.15; 95% CI: 1.37; 3.36). The association between mistreatment perceived as severe and dissatisfaction with the course (PR = 1.67; 95% CI: 0.94; 2.99) reached a borderline significant level (P = 0.07).

DISCUSSION

This was the first study to take a systematic approach towards investigating exposure to recurrent mistreatment and mistreatment perceived as severe and their associations with students' perceptions about their medical course in a Brazilian medical school. Students in their first to sixth year were enrolled, and data were collected using an online system that guaranteed full anonymity and confidentiality. We used a structured questionnaire to measure mistreatment, classified according to frequency and perceived severity.

Participation was not mandatory, and we had a fair response rate (31.5%). Our final sample represented 29.45% of the total original population (n = 317). Low response rates seem to be a problem common to many web-based surveys.[22,23] In an online survey concerning negative experiences during medical education at the University of Göttingen, in Germany, a similar response rate of 32% was found.[10] Since participation in our survey was not mandatory, the possibility of selection bias also has to be borne in mind: this might have resulted either in overestimation of our prevalence estimates (since voluntary surveys attract the attention of those more interested in or affected by the topic) or even in underestimation (because the response rates were lower among the students in their clinical years/internship, when occurrences of mistreatment tend to be more frequent).

It is impossible to know whether those who participated in this study were more or less exposed to mistreatment, but our results are consistent with those reported by other studies. Furthermore, our final sample had more women and fewer clinical-year students than a reference population. To address this imbalance, we used post-stratification weighting for sex and

Table 2. Exposure to mistreatment and negative perceptions about the medical course in São Paulo, Brazil, 2013

Variable	Total		School cycle						P-value linear trend in χ^2 test
			Basic		Preclinical		Clinical		
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Mistreatment									
Overall	92.3	(88.5; 94.9)	90.2	(83.7; 94.3)	91.2	(83.2; 95.6)	95.7	(87.2; 98; 6)	0.26
Recurrent	30.1	(24.9; 35.9)	24.9	(18.3; 33.0)	28.2	(20.2; 37.8)	37.2	(26.5; 49.3)	0.06
Severe	64.2	(58.4; 69.6)	57.5	(49.0; 65.6)	63.8	(53.9; 72.7)	71.4	(59.3; 81.1)	0.04
Negative perceptions about the course									
Feeling overloaded	80.3	(75.0; 84.7)	83.7	(76.3; 89.1)	75.5	(65.9; 83.1)	81.7	(69.9; 89.5)	0.74
Feeling dissatisfied	19.6	(15.4; 24.5)	21.1	(15.1; 28.7)	16.1	(10.0; 24.9)	21.5	(13.6; 32.2)	0.78
Considering dropping out	34.3	(28.9; 40.1)	29.1	(22.1; 37.4)	36.6	(27.7; 46.6)	37.1	(26.4; 49.1)	0.15
Poor academic achievement	43.4	(37.8; 49.3)	57.8	(49.3; 65.8)	39.5	(30.3; 49.5)	32.9	(22.9; 44.9)	0.08

CI = confidence interval.

Table 3. Association between recurrent or severe mistreatment and negative perception about the medical course in São Paulo, Brazil, 2013

	Feeling overloaded		Feeling dissatisfied		Willingness to drop out		Poor academic achievement	
	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
Recurrent mistreatment								
Crude	1.06	(0.94; 1.20)	1.14	(0.69; 1.87)	1.33	(0.95; 1.86)	1.08	(0.81; 1.44)
Adjusted*	1.08	(0.96; 1.23)	1.16	(0.70; 1.92)	1.29	(0.92; 1.81)	1.14	(0.86; 1.51)
Severe mistreatment								
Crude	**1.2**	**(1.04; 1.39)**	1.67	(0.95; 2.09)	**2.16**	**(1.39; 3.36)**	1.24	(0.92; 1.65)
Adjusted*	**1.17**	**(1.02; 1.36)**	1.67	(0.94; 2.99)	**2.15**	**(1.37; 3.36)**	1.27	(0.95; 1.69)

PR = Poisson logistic regression. Model adjusted for gender, age, skin color, whether student was admitted to course through the social inclusion policy and school cycle; CI = confidence interval.

school year, with adjustments for all point and interval estimates. It is important to note that this was a cross-sectional study, and it was not possible to ascertain whether the mistreatment occurred prior to the development of negative perception about the medical course.

Exposure to mistreatment that was considered severe was positively associated with perceived overload and willingness to drop out of the course. The exposed students reported feeling overwhelmed more frequently than did those who were not exposed, and expressed willingness to drop out of the course more frequently than did those who were not exposed, even after adjusting for potential confounders. These results support our hypothesis that there would be an independent association between exposure to mistreatment that was perceived as severe and negative perceptions about the course.

Prevalence of exposure to violence

According to our results, nearly every student suffered at least one form of mistreatment during the medical course. The overall prevalence was extremely high, making it evident that this phenomenon is present in the everyday life of students and plays an important role in the academic environment in medical school, within all school cycles. Even when only the cases that were judged to be severe and those that were recurrent (five times or more during the course) were taken into consideration, the prevalence was high. According to our results, exposure to mistreatment became higher as the course progressed, thus reflecting the cumulative dimension of our measurement. We were unable to ascertain the time when mistreatment occurred with any certainty, since our questionnaire asked about experiences at any time during the course. However, the high prevalence found during the basic years reflects exposure during the first two years of medical training, a period when students might be especially vulnerable to the consequences of mistreatment, given that they enter the medical course early in life in Brazil, immediately following high school and with no previous experience of college or university dynamics.

Similar high figures have previously been described in the United States,[1,5] Chile,[3] Nigeria[12] and Germany.[10] According to Baldwin et al.,[1] 96.5% of the students in the fourth and fifth years in 10 medical schools in the United States reported having had exposure to at least one type of mistreatment (assault, harassment or mistreatment) during the course. More recent results reported by Frank et al.[5] have indicated that the prevalence remains high: 84% of the students reported having been belittled during the course in a study conducted in 16 US medical schools. In Nigeria, Chile and Germany, the overall prevalences were, respectively, 98.5%, 91.5% and 88%. A recent meta-analysis[24] reported that the pooled prevalence of harassment and discrimination among medical students was of the order of 59.6% (95% CI: 49.2%; 68%) and that the pooled prevalence of verbal harassment was 68.8% (95% CI: 56.6%; 80.9%).

Lower prevalence of mistreatment has been reported in relation to episodes of bullying characterized by recurrent violence. In Saudi Arabia, Alzahrani[9] reported that the prevalence of bullying was 28% among medical students, whereas in Pakistan, the prevalence was 52% among sixth-year medical students.[6] In Colombia, Paredes et al.[8] reported that the prevalence of bullying was 19.7%. In our study, 30.1% of the students reported a pattern of repeated exposure to mistreatment (> 5 episodes) during the course.

It is noteworthy that such high prevalence persists and is widespread in so many different countries and scenarios. In the early 1990s, following the study published by Sheehan et al.,[15] the high prevalence of assault, abuse and harassment in medical education was brought to light, as was the existence of a cycle of abusive practices that had been incorporated as a "necessary part" of medical education. According to Fried et al.,[14] the high frequency of abuse, mistreatment and other forms of aggression within medical courses demonstrates the existence of a strongly hierarchical medical culture that permeates the relationship between teachers and students, thus perpetuating situations of maltreatment as "rites of passage". According to our data, this pattern of relationship is present starting from the first years of medical education and persists throughout the course. This culture is, according to Kay,[25] a problem that goes beyond the undergraduate years and persists over time in different spaces of medical training, where attending physicians, supervisors, residents and students reproduce the abuse and mistreatment suffered during the formative years in a cycle that feeds itself.

Consequences of mistreatment on the way students perceive medical education

The existence of a pattern of relationships based on humiliation and psychological violence, both between students and in teaching relationships, may negatively affect the way in which students perceive medical education and professional choice.[5,16,20] Our results brought to light that a high proportion of students have negative perceptions about the course, especially during the basic cycle, in which the figures were higher for all indicators except for considering dropping out of the course, which was seen more frequently during the clinical cycle. This may be a reflection of the cumulative dimension of this specific measurement, since we asked whether the students had ever considered dropping out the course. Feeling overloaded, being dissatisfied and having poor academic achievement were all related to the students' experiences and thus these characteristics closely reflect the students' actual experience with the course. In this sense, it is quite

surprising that in the basic cycle, the figures were of such high magnitude. This can be explained by the early age at which the students started their training in such a hard and demanding course as medical education, with the need to deal with academic stress, the strong hierarchy mentioned previously and occurrences of mistreatment.

It should be noted that according to our results, episodes of mistreatment are not only highly prevalent but also recurrent and are judged to be severe by the students. Our results demonstrate that the mistreatments that the students considered to be severe were associated with negative impressions about the course. Feeling overwhelmed and considering dropping out of the course were seen more frequently among those who judged the mistreatment to be severe, even after adjustment for potential confounders.

Rosenberg[16] described the negative consequences of mistreatment on academic achievement and subsequent professional conduct in the 1980s. According to these authors, abuse is related to poorer learning, lower self-esteem and lower quality of patient care. Recent studies have indicated that students who have been the victims of abuse, maltreatment or other forms of aggression are more dissatisfied with their career choice, are more likely to consider dropping out and report poorer relationships with teachers.[5] According to Timm,[11] students who have been exposed to bullying or harassment find it harder to concentrate and are less satisfied with their career choice. Mistreatment also has consequences for students' mental health. Those who are exposed feel more stressed and depressed, have low self-esteem and are more likely to consume alcohol and binge-drink.[5,7,12,17-19]

The different sources of stress to which medical students are exposed during their medical training are well known.[18,26,27] Medical education is hard to access and difficult to sustain, given the large amount of time dedicated to academic activities and the amount of suffering and distress that students need to cope with on a daily basis. Overwhelming activities, along with contact with disease and death early in life, are among the factors that explain the high prevalence of depression and burn-out and the perception of poor quality of life that are commonly reported in medical student surveys.[28-34]

According to Dyrbey et al.,[35] unprofessional conduct and less altruistic professional values are more common among students with burn-out, thus suggesting that distress during medical education may compromise quality of care. Similar results were found in a study involving 1098 medical students in the United States,[36] in which distress and lack of wellbeing were shown to present connections with lack of empathy among medical students. In the same study, perceptions of personal accomplishment and high quality of life were both associated with higher empathy.

Despite the fact that mistreatment has been found to be highly prevalent in different countries and during different time periods, this study provided the first systematic approach towards this topic in a Brazilian medical school. It should be noted that this is an opportune time to bring this discussion to the forefront in this country, because the new national curriculum guidelines that were recently approved state that medical schools should be able to provide training for doctors to practice "general, humanistic, critical, reflective and ethical medicine (…) with social responsibility and commitment to the defense of citizenship [and] human dignity".[37] Considering the negative impact of mistreatment on mental health and wellbeing, and the way in which students perceive their course and academic achievements,[5,7,12,16-20] occurrences of mistreatment during medical training have high potential to compromise quality of care and the way in which students approach their patients and their suffering. Mistreatment represents an additional source of stress for medical students that should be seriously taken into consideration by medical schools.

CONCLUSION

Mistreatment is highly prevalent within medical education in Brazil, Mistreatment that is perceived as severe by students has a negative impact on the way in which they perceive their course. In our study, however, recurrent mistreatment per se was not associated with negative perceptions about the course or poor academic achievement.

Our results suggest that the subjective dimension of mistreatment (i.e. the students' perceptions regarding its severity) is more important than recurrence, in considering the impact on the way in which students perceive their course, and this should be taken into considered in future investigations.

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Source of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP): research grant no. 2013/11989-3; undergraduate research scholarships from FAPESP (grant nos. 2013/08795-2 and 2013/08788-6); and undergraduate research scholarship from the institutional program for undergraduate research scholarships of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (PIBIC/CNPq)
Conflict of interests: None

Congress: Partial results from this research were presented at the 33rd Medical Congress of the University of São Paulo Medical School (Congresso Médico Universitário da FMUSP, COMU) and at the 52nd Brazilian Congress of Medical Education (Congresso Brasileiro de Educação Médica, COBEM)

Awards received: First place in the Oswaldo Cruz award for clinical medicine, at the 33rd COMU. Second place in the oral presentation category at the 52nd COBEM

Date of first submission: July 3, 2015
Last received: October 9, 2015
Accepted: October 22, 2015

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DOI: 10.1590/1516-3180.2015.01691609

Meat intake among adults: a population-based study in the city of Campinas, Brazil. A cross-sectional study

Ingestão de carnes em adultos: estudo de base populacional na cidade de Campinas, Brasil. Um estudo transversal

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KEY WORDS:
Meat.
Health surveys.
Adult.
Eating.
Diet.

PALAVRAS-CHAVE:
Carne.
Inquéritos epidemiológicos.
Adulto.
Ingestão de alimentos.
Dieta.

ABSTRACT

CONTEXT AND OBJECTIVE: Meat is a food with high nutritional density that has significant participation in the Brazilian diet. However, in excess it can cause harm to health. The aim of this study was to analyze the meat intake (g/day) among adults according to sociodemographic, behavioral and health situation characteristics, and to assess the types of meat most consumed.

DESIGN AND SETTING: Cross-sectional population-based study conducted in the city of Campinas, São Paulo, Brazil, in 2008 and 2009.

METHODS: Two-stage cluster sampling was used. The analysis included 948 adults between 20 and 59 years, who were participants in the Campinas Health Survey. Meat intake was assessed using 24-hour dietary recall.

RESULTS: The mean meat intake adjusted for sex and age was 182.3 g (95% CI: 170.6-193.9 g), with significantly lower intake among women, individuals aged 50 years or over, those with the presence of two or more self-reported chronic diseases and those with three or more health complaints. Higher meat intake was found in segments with intermediate monthly family income (between 1 and 3 minimum wages), those with 16 or more appliances per household and those who consumed soft drinks seven days a week. Beef was consumed most frequently (44%) among the meats in the diet, followed by poultry, fish and pork.

CONCLUSION: The data from this study reveal high meat intake in the population of Campinas and identify the segments that need to be prioritized for strategies directed towards appropriate meat intake.

RESUMO

CONTEXTO E OBJETIVO: As carnes são alimentos com elevada densidade nutricional, apresentam expressiva participação na dieta dos brasileiros, porém em excesso provocam prejuízos à saúde. O objetivo deste estudo foi analisar a ingestão de carnes (g/dia) entre adultos segundo características sociodemográficas, comportamentais e de situação de saúde, além de avaliar os tipos de carnes mais consumidos.

DESENHO E LOCAL: Estudo transversal de base populacional, realizado em Campinas, SP, Brasil, em 2008 e 2009.

MÉTODOS: A amostra foi obtida por conglomerados e em dois estágios. Foram analisados 948 adultos (20-59 anos), participantes do Inquérito de Saúde de Campinas. O recordatório alimentar de 24 horas foi utilizado para estimar a ingestão de carnes.

RESULTADOS: A ingestão média de carnes ajustada por sexo e idade foi de 182,3 g (IC 95%: 170,6-193,9 g), sendo significativamente menor nas mulheres, nos indivíduos com 50 anos ou mais, nos que relataram duas ou mais doenças crônicas e nos que apresentavam três ou mais queixas de saúde. Maior ingestão de carnes foi encontrada nos segmentos com renda familiar mensal intermediária entre 1 e 3 salários mínimos, com 16 ou mais equipamentos no domicílio, assim como aqueles que ingeriam refrigerantes nos 7 dias da semana. A carne bovina foi a mais frequente (44%) entre as carnes presentes na dieta, seguida de aves, processadas, peixes e suínas.

CONCLUSÃO: Os dados desta pesquisa revelam elevada ingestão de carnes na população de Campinas e identificam os segmentos que devem ser priorizados para estratégias direcionadas a adequar a ingestão desse alimento.

INTRODUCTION

Meat is a food group with significant participation in the Brazilian diet, and is used in the main course of most meals. It is a food with high nutrient density that provides an important source of high-quality proteins, vitamins and minerals for the Brazilian population, especially as a source of vitamin B12 and heme-iron.[1]

Brazil is also the second largest producer of beef in the world, and ranks highly with regard to production levels of other meats like chicken and pork.[2,3]

According to a national dietary survey, the Brazilian meat intake corresponds to 151.8 g/day.[4] Compared with other foods, meat has greater participation than fruits (86.1 g/day), vegetables (24.6 g/day) and legumes (40.7 g/day), thus demonstrating its significant participation and intake.[4] Other Brazilian surveys have also indicated that meat intake has increased over the years.[5] Between the periods of 1974-1975 and 2002-2003, the participation of meat in the diet increased by almost 50%.[6]

The Brazilian Ministry of Health recommends that the maximum total meat intake should be 100 g per day, which corresponds to a portion of 190 kcal.[7] The latest Brazilian dietary guidelines also emphasize that unprocessed lean meat should form part of a nutritionally adequate diet and it is recommended that the intake of red and processed meat should be reduced.[1]

The World Cancer Research Fund International (WCRF) has established a maximum recommendation of 500 g for red and processed meat per week,[8] since these are the types of meat with higher quantities of cholesterol and saturated fat. These types of meat have been described in longitudinal analyses as risk factors for chronic diseases such as colorectal cancer,[8] type 2 diabetes mellitus,[9] atherosclerosis and other cardiovascular diseases.[10,11]

OBJECTIVE

Given the importance of meat intake within the national scenario and the potential problems relating to excessive meat intake, the objective of this study was to describe the average meat intake (g/day) among adults ages 20-59 years old in the city of Campinas, São Paulo, Brazil, according to sociodemographic variables, health-related behavior, morbidities and body mass index (BMI); and also to identify the types of meat consumed by this population.

METHODS

This was a cross-sectional population-based study developed using data from the Campinas Health Survey (ISACAMP 2008/2009), which obtained information from non-institutionalized individuals who were living in the urban area of the city of Campinas between February 2008 and April 2009.

The survey sample was determined through two-stage cluster sampling. In the first stage, 50 census tracts with probability proportional to size (number of households) were drawn. Considering the time that had elapsed since the census of 2000, addresses of selected tracts were updated. In the second stage, households were drawn.

The population was divided into three age domains: adolescents (10-19 years), adults (20-59 years) and elderly people (60 years or over). Independent samples of 1,000 people in each domain were drawn, taking into consideration the maximum variability of the frequencies of the events studied (P = 0.50), 95% confidence level, sampling error of between 4 and 5 percentage points and a design effect of 2. To obtain the desired sample size while taking into account the predicted non-response rate of 20%, 2,150, 700 and 3,900 households were drawn for interviews with adolescents, adults and elderly people, respectively. The estimated number of households was calculated based on the person/household ratio in each age domain. The interviews were conducted directly with residents within the age group drawn for that specific household. For this study, we used data on adults of both genders.

The information was collected by means of a questionnaire that was structured into 14 thematic blocks and had been tested in a pilot study. It was administered by trained and supervised interviewers. The thematic block relating to dietary habits included a food frequency questionnaire, self-reported weight and height and one 24-hour dietary recall, in which the respondents reported all the foods and beverages eaten the day before the interview. Interviews covering different days of the week and months of the year were collected.

The 24-hour dietary recall was quantified so as to convert homemade measurements to grams or milliliters, using information available from homemade measurement tables,[12,13] food labels and customer service centers.

The data from the 24-hour dietary recall were entered into the Nutrition Data System for Research, 2007 version (NCC Food and Nutrient Database, University of Minnesota, Minneapolis, MN, USA).

Study variables

The dependent variable was the mean meat intake (g/day).

The set of independent variables analyzed was the following.

Socioeconomic and demographic information: gender, age (in years), education level (in years of school attendance), per capita household income (in numbers of minimum wages) and number of appliances in the household.

Health-related behavior: weekly frequency of fruit, vegetable and soft-drink consumption; smoking and alcohol consumption.

Morbidities and body mass index (BMI): self-reported number of chronic diseases that had been diagnosed by a doctor (hypertension, diabetes, cancer, arthritis, osteoporosis, asthma, tendonitis and circulation problems) and number of health

complaints among the ones included in the checklist (such as frequent migraines, back pain, allergies, etc.). The BMI was calculated using self-reported weight and height. Nutritional status was classified in accordance with the World Health Organization's recommendation for adults:[14] underweight BMI < 18.5 kg/m^2, eutrophic BMI between 18.5 and 24.9 kg/m^2, overweight BMI between 25.0 and 29.9 kg/m^2 and obese BMI ≥ 30 kg/m^2.

The average meat intake was estimated and differences between the means of the subgroups investigated were ascertained by means of simple and multiple linear regression, considering a 5% significance level for associations with the variables analyzed. The means were adjusted for age and sex.

Meat was classified according to animal origin and the type of processing, as follows: beef, poultry, pork, fish and processed meat, i.e. meat of any animal origin that had been subjected to industrial processing, so as to manufacture sausages, hamburgers, nuggets and other meat products. The relative participation of meats in the diet was calculated by dividing the total for each meat group (g) by the total meat in the diet (g). The mean intake of the separate types of meat was also calculated, using the following four categorizations: red and processed; poultry; fish; and pork.

The interviews were typed into the database using Epidata 3.1 (Epidata Assoc., Odense, Denmark) and statistical analyses were done using the survey module of the Stata 11.0 software (Stata Corp., College Station, USA), which enables analysis on data from complex samples.

The project ISACAMP 2008 was approved by the Research Ethics Committee of the School of Medical Sciences at the State University of Campinas under the protocol no. 079/2007.

RESULTS

In the present study, 957 adults were interviewed. Among these, 9 individuals refused to participate in the 24-hour dietary recall, and therefore 948 adults were evaluated, including 43 who did not report eating meat on the day before the interview. Females accounted for 504 individuals and males for 444. The participants' mean age was 37.5 years (95% CI: 36.6-38.3): 37.9 years for females (95% CI: 36.9-38.8) and 37.0 years for males (95% CI: 36.0-38.0).

The mean energy intake in the study was 2,013.27 kcal (95% CI: 1,934.95-2,091.39). The mean energy intake for males was 2,290.42 kcal (95% CI: 2,169.78-2,411.05) and for females, 1,750.08 kcal (95% CI: 1,669.80-1,830.36).

Considering the types of meat, the mean meat intake comprised 73.8 g (95% CI: 69.6-78.0) for red and processed meats; 97.6 g (95% CI: 86.9-108.4) for poultry; 69.7 g (95% CI: 52.7-86.6) for pork; and 86.6 g (95% CI: 62.5-110.7) for fish.

The most prevalent type of meat consumed was beef (41%), followed by poultry (22.8%), processed (16.8%), fish (8.4%) and pork (7.9%).

The daily mean total meat intake was 191 g (95% CI: 179.1-202.8), and the intake was significantly lower among women, and among individuals aged 50 years or over, compared with those between 20 and 29 years of age. Meat was more often consumed among individuals who reported per capita family incomes of between one and three minimum wages, and among those who had 16 or more appliances in the household (**Table 1**).

Table 2 shows that elevated meat consumption was associated with intake of soft drinks seven days a week, but that no other health-related behavioral patterns showed significant associations.

Table 3 shows that there was lower meat intake among individuals with two or more chronic diseases. Individuals who reported the presence of three or more health complaints also had statistically lower meat intake.

DISCUSSION

The most important results from this study were that there was high dietary intake of meats among males and among individuals who reported monthly income of 1 to 3 minimum wages, those who had 16 or more appliances in the household and those who drank soft drinks on a daily basis. On the other hand, lower meat intake was observed among individuals aged 50-59 years than among those aged 20-29 years, and among individuals who reported the presence of two or more chronic diseases and those with three or more health complaints.

A separate analysis on the types of meat demonstrated that the highest intake was attributed to poultry, followed by red and processed meats. Higher demand for poultry has also been observed in the American population.[15] The current literature does not demonstrate any higher incidence of colorectal cancer when the lean meat intake is within the recommended amounts.[16,17] The American Heart Association recommends a maximum of 170 g of lean meat per day, which includes cooked poultry without skin and fish as important sources of high-quality protein in the diet.[18]

On the other hand, red and processed meats have been demonstrated to be risk factors for cardiovascular diseases[9,11] and colorectal cancer.[16,17] The findings relating to pork remain contradictory, since this meat has been shown to have no effect on metabolic syndrome,[19] while its effect on colorectal cancer is unclear.[17] At the same time, this meat type is usually analyzed inside the red meat subgroup,[9] thus participating in the same group as beef and lamb in most analyses.

Furthermore, considering the distribution of the types of meat, there was greatest participation by beef, poultry and processed meats. Levy et al. worked on the Brazilian Household Budget Survey (BHBS) in 2008-2009 and observed

Table 1. Mean meat intake (g/day) according to demographic and socioeconomic variables among adults between 20 and 59 years of age. Campinas Health Survey (ISACAMP, 2008/2009)

Variables	n	Mean in g/day (95% CI)	P-value	Adjusted mean in g/day* (95% CI)	P-value
Gender					
Male†	444	283.8 (253.0-314.6)		291.5 (258.2-324.8)	
Female	504	216.8 (170.4-263.1)	**0.000**	224.5 (17.57-263.3)	**0.000**
Total	948	182.3 (170.6-193.9)			
Age group (in years)					
20 to 29†	302	192.7 (174.9-210.4)		291.5 (258.2-324.8)	
30 to 39	231	185.2 (144.6-225.7)	0.508	289.0 (233.5-344.5)	0.821
40 to 49	220	177.4 (137.2-217.7)	0.179	281.4 (225.2-337.7)	0.382
50 to 59	195	167.3 (127.8-206.8)	**0.023**	267.6 (212.3-322.9)	**0.034**
Education (in years)					
0 to 7†	272	173.6 (155.1-192.2)		287.8 (249.2-326.4)	
8 to 11	398	186.9 (143.7-230.2)	0.284	293.3 (229.7-356.9)	0.660
12 and over	278	183.7 (141.6-225.7)	0.397	289.7 (227.9-351.6)	0.867
Per capita family income (in minimum wages)					
< 1†	376	165.1 (150.8-179.3)		273.3 (239.8-306.8)	
≥ 1 to ≤ 3	393	197.0 (160.8-233.3)	**0.005**	300.3 (245.2-355.3)	**0.015**
> 3	179	184.9 (140.4-229.5)	0.195	292.4 (230.4-354.5)	0.185
Number of appliances in the household					
1 to 10†	394	172.5 (156.6-188.4)		282.2 (250.1-314.3)	
11 to 15	304	186.1 (148.2-224.0)	0.221	298.7 (244.7-352.6)	0.134
16 and over	248	193.3 (153.3-233.4)	0.090	309.2 (254.4-364.0)	**0.020**

CI = confidence interval; *adjusted for age and/or sex; †reference category.

Table 2. Mean meat intake (g/day) according to health-related behavior among adults between 20 and 59 years of age. Campinas Health Survey (ISACAMP, 2008/2009)

Variables	n	Mean in g/day (95% CI)	P-value	Adjusted mean in g/day* (95% CI)	P-value
Fruit consumption (times a week)					
7†	346	174.4 (160.0-188.8)		291.9 (258.3-325.4)	
4 to 6	159	179.3 (132.6-225.9)	0.764	287.5 (221.6-353.3)	0.786
≤ 3	442	189.4 (155.2-223.5)	0.136	292.5 (239.4-345.6)	0.948
Vegetable consumption (times a week)					
7†	460	189.0 (174.1-203.9)		303.7 (271.1-336.3)	
4 to 6	214	175.1 (137.5-212.7)	0.223	285.4 (230.3-340.5)	0.108
≤ 3	273	176.2 (137.4-214.9)	0.286	284.3 (229.0-339.6)	0.092
Soft-drink consumption (times a week)					
≤ 3†	656	172.7 (160.2-185.2)		280.0 (246.3-313.7)	
4 to 6	86	191.7 (149.3-234.2)	0.209	291.0 (229.9-352.2)	0.422
7	205	208.6 (172.9-244.3)	**0.003**	307.7 (251.8-363.5)	**0.015**
Smoking					
Never smoked†	642	186.6 (172.8-200.4)		297.6 (263.2-331.9)	
Former smoker	109	165.6 (124.2-206.9)	0.131	276.2 (215.4-336.9)	0.109
Smoker	195	177.7 (143.0-212.3)	0.393	281.5 (227.4-335.6)	0.108
Alcohol consumption					
Does not drink†	327	195.7 (177.9-213.4)		297.9 (262.6-333.1)	
Drinks 1 to 4 times a month	496	170.1 (132.7-207.4)	**0.011**	285.6 (230.6-340.5)	0.218
Drinks 2 or more times a week	123	195.6 (154.4-236.8)	0.997	283.7 (223.9-343.5)	0.253

CI = confidence interval; *adjusted for age and sex; † reference category.

that beef (4.42%), chicken (4.03%) and processed meat (2.22%) were the meats with highest participation in the national diet.[20] Daniel et al. studied the American population and found similar distribution: 58% of the meat intake consisted of red meat (beef and pork), 32% poultry and 10% fish; processed meats were analyzed separately and corresponded to 22% of the overall meat intake.[21]

The average meat consumption of the population of Campinas (182.3 g) is higher than the national average. Evidence from the BHBS (2008/2009) showed that the national per capita meat intake was 151.8 g/day.[4] Meat intake in Campinas was also greater than the total meat intake of 136.5 g found by Carvalho et al. in the city of São Paulo.[22] Data from the National Health and Nutrition Examination Survey (NHANES) 2003 found that the average meat intake in the American population aged 20-49 years was 141 g/day, thus demonstrating that meat consumption in Campinas is high in comparison with national and international realities.[21]

Regarding gender differences, men were found to eat 67 g more meat than women. Other Brazilian studies have also indicated greater meat intake among men, especially for beef.[4,5,22] Data from a telephone survey conducted in Brazil showed that men ate twice as much meat with visible fat as women did.[23] This gender difference is related to the female concern for healthier food choices. Females are cautious about calories and fat content and usually select a diet with more fruits and vegetables instead of meat.[24,25]

Individuals aged 50 to 59 years had significantly lower meat intake than those aged 20-29 years, and this result was similar to what was found in NHANES.[21] The Brazilian telephone survey of 2013 also revealed that meat consumption was lower among older individuals.[23] Aging is accompanied by a greater risk of chronic diseases, which may influence individuals to improve their food choices and seek guidance from healthcare services, where disease control information is available.[26]

Regarding socioeconomic factors, higher dietary meat intake in the intermediate stratum of income was also observed by Carvalho et al. in the city of São Paulo.[22] This pattern of meat intake among individuals with average income is associated with a trend towards eating meat as their income improved. The number of appliances in the household is considered to be a proxy variable for income, and it was observed that the individuals in the intermediate stratum of income were the ones with the greatest number of appliances in the household, thus explaining the greater meat intake in these categories.

Researchers using data from NHANES 2003 evaluated education levels as a proxy indicator for income, and demonstrated the same distribution of meat intake.[21] This behavior indicates that the price of meat is still the determinant for access among lower-income populations.

Meat intake has shifted with the nutritional transition and the urbanization process, which has reduced the cost of meat based on government investment in livestock. This change has allowed lower-income individuals to purchase more meat, thereby bringing good protein and micronutrient sources into their diet. On the other hand, there have been increases in meat intake among individuals whose socioeconomic situation has improved, since meat has become much more attractive than fruits and vegetables because of its reduced price.[27] Meat intake is linked to anthropological and symbolic factors regarding the status of eating meat and this also explains why income is an associated factor.[28,29]

The association between soft drinks and meat intake can also be explained by the change in cost. It also relates to urbanization and the nutritional transition, since the intake of

Table 3. Mean meat intake (g/day) according to morbidities and body mass index among adults between 20 and 59 years of age. Campinas Health Survey (ISACAMP, 2008/2009)

Variables	n	Mean in g/day (95% CI)	P-value	Adjusted mean in g/day* (95% CI)	P-value
Number of chronic diseases					
0†	588	195.4 (181.9-208.8)		291.9 (258.1-325.8)	
1	227	172.0 (140.3-203.6)	**0.013**	274.2 (221.9-326.7)	0.061
2 and over	123	138.9 (99.2-178.6)	**0.000**	252.6 (190.4-315.0)	**0.008**
Number of health complaints					
0†	283	193.9 (176.1-211.6)		284.4 (251.0-317.7)	
1 or 2	453	192.4 (154.2-230.5)	0.880	295.2 (240.6-349.8)	0.311
3 and over	212	144.1 (104.0-184.1)	**0.000**	258.7 (201.3-316.0)	**0.036**
BMI (kg/m^2)					
Eutrophic/ underweight†	486	181.7 (168.1-195.3)		295.3 (264.7-325.8)	
Overweight	299	187.9 (156.6-219.3)	0.483	300.1 (252.1-348.1)	0.583
Obesity	143	173.3 (134.2-212.4)	0.511	294.4 (237.7-350.8)	0.941

CI = confidence interval; *adjusted for age and sex; †reference category.

sugar-sweetened beverages has increased with the reduction in cost of sugar as a commodity and the popularization of these beverages in the Western diet.[27]

The lower meat intake among individuals with two or more chronic diseases and among those with three or more health complaints can be discussed based on the results from Barreto and Figueiredo, who found that the intake of meat with visible fat was inversely associated with the presence of one or more chronic diseases among adults of both genders. This was due to the behavioral change that usually occurs after a chronic disease has been diagnosed. The presence of chronic diseases increases attendance at healthcare services, where individuals receive information relating to health and nutrition. This is usually accompanied by lifestyle modifications in order to minimize the consequences of a disease.[30]

One of the limitations of the present study arose from the application of a single 24-hour dietary recall, which thus did not allow this study to assess the usual diet and limited the possibility of assessing intraindividual variability. Nevertheless, although only one 24-hour recall was collected, these recalls were conducted on different days of the week, and also included weekends and different months of the year, thereby reducing interindividual variabilities.[31] The 24-hour dietary recall within ISACAMP 2008/2009 was administered to a representative sample of the population of Campinas and therefore enables estimation of the consumption of meat for the city's population.

Another limitation of the present study was the self-reporting of information on the presence of chronic diseases that had been diagnosed by a physician, and of height and weight data. Although this constitutes a limitation, Almeida et al.[32] concluded that such information is consistent, through comparing individuals' self-reported prevalence of chronic diseases and self-assessment of health with the observed impairment of individuals' daily activities and the existence of situations of being bedridden.[32] Concerning the use of self-reported height and weight information, epidemiological surveys commonly use self-reported information,[5] and such data has been shown to be valid.[33] A study on a similar population demonstrated good comparability between assessed and reported height and weight information among adults.[34]

In addition, since this was a cross-sectional analysis, it provided a snapshot of the population at a single time and associations based on cause and effect cannot be predicted.

CONCLUSION

In the population of Campinas, the individuals whose meat intake was higher were male, younger adults, individuals with an intermediate family income, those with daily soft-drink intake and those who presented fewer chronic diseases and health complaints. All of these groups presented high average total meat intake, compared with the findings from Brazilian studies and studies in other countries. Furthermore, red meat was the most prevalent type of meat consumed.

The conclusions of this study demonstrate that there is a need for public health interventions from clinicians and researchers with the aims of providing information on the recommended total meat intake and of counseling patients regarding the health risks of high intake of red and processed meats and the importance of choosing lean meats as part of a healthy diet.

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Sources of funding: Ministério da Ciência, Tecnologia e Inovação, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 409747-2006-8)
Conflict of interests: None

Date of first submission: May 5, 2015
Last received: September 11, 2015
Accepted: September 16, 2015

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DOI: 10.1590/1516-3180.2015.02040211

Alcohol consumption during pregnancy and perinatal results: a cohort study

Consumo de álcool durante a gravidez e resultados perinatais: um estudo de coorte

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KEY WORDS:
Alcohol drinking.
Pregnancy.
Infant, low birth weight.
Infant, small for gestational age.
Premature birth.

PALAVRAS-CHAVE:
Consumo de bebidas alcoólicas.
Gravidez.
Recém-nascido de baixo peso.
Recém-nascido pequeno para a idade gestacional.
Nascimento prematuro.

ABSTRACT

CONTEXT AND OBJECTIVE: Alcohol consumption during pregnancy is a significant social problem that may be associated with adverse perinatal outcomes. The aim of this study was to describe alcohol consumption during pregnancy and to study its association with low birth weight, newborns small for gestational age and preterm birth.

DESIGN AND SETTING: Nested cohort study, in the city of Ribeirão Preto, São Paulo, Brazil.

METHODS: 1,370 women and their newborns were evaluated. A standardized questionnaire on health and lifestyle habits was applied to the mothers. Anthropometry was performed on the newborns. Alcohol consumption was defined as low, moderate or high, as defined by the World Health Organization. Adjusted logistic regression analysis was used.

RESULTS: 23% of the women consumed alcohol during pregnancy. Consumption mainly occurred in the first trimester (14.8%) and decreased as the pregnancy progressed. The median alcohol intake was 3.89 g (interquartile range, IQR = 8 g) per day. In the unadjusted analysis, alcohol consumption increased the risk of low birth weight almost twofold (odds ratio, OR 1.91; 95% confidence interval, CI: 1.25-2.92). The risk was lower in the adjusted analysis (OR 1.62; 95% CI: 1.03-2.54). Alcohol consumption did not show associations with small for gestational age or preterm birth. There was greater risk of low birth weight and newborns small for gestational age and preterm birth among mothers who were both smokers and drinkers.

CONCLUSIONS: The alcohol consumption rate during pregnancy was 23% and was independently associated with low birth weight, but there was no risk of newborns small for gestational age or preterm birth.

RESUMO

CONTEXTO E OBJETIVO: O consumo de álcool durante a gravidez é um problema social significativo que pode estar associado a resultados perinatais adversos. O objetivo deste estudo foi descrever o consumo de álcool na gestação e avaliar sua associação com recém-nascido de baixo peso, pequeno para idade gestacional e pré-termo.

TIPO DE ESTUDO E LOCAL: Estudo de coorte aninhado, na cidade de Ribeirão Preto, São Paulo, Brasil.

MÉTODOS: Foram avaliadas 1.370 mulheres e seus recém-nascidos. Foi aplicado às mães um questionário padronizado sobre saúde e hábitos de vida. Antropometria foi realizada nos recém-nascidos. Consumo de álcool foi definido como baixo, moderado e elevado segundo a Organização Mundial de Saúde. Foi utilizada análise de regressão logística ajustada.

RESULTADOS: 23% das gestantes consumiram álcool durante a gravidez. A maior parte do consumo ocorreu no primeiro trimestre (14,8%) e diminuiu conforme progredia a gravidez. A mediana de ingestão de álcool foi de 3,89 g (interval interquartil, IIQ = 8 g) por dia. Na análise não ajustada, o consumo de álcool aumentou em quase duas vezes (*odds ratio*, OR 1,91, intervalo de confiança, IC 95%; 1,25-2,92) o risco de baixo peso, que se reduziu após ajuste (OR 1,62; IC 95%; 1,03-2,54). Não houve associação entre consumo de álcool e pequeno para idade gestacional ou pré-termo. Observou-se maior risco de baixo peso, neonato pequeno para idade gestacional e pré-termo em gestantes simultaneamente fumadoras e bebedoras.

CONCLUSÕES: O consumo de álcool na gestação foi de 23% e esteve associado independentemente com o baixo peso ao nascer, mas não houve risco para neonato pequeno para idade gestacional e pré-termo.

INTRODUCTION

Alcohol consumption during pregnancy is a significant social problem that may be associated with adverse perinatal outcomes such as low birth weight (LBW), small for gestational age (SGA) or preterm newborns.[1] However, the relationship between alcohol consumption during pregnancy and adverse perinatal outcomes is still controversial. While some studies have detected higher percentages of LBW, SGA and preterm birth among infants exposed to alcohol during pregnancy,[2-5] others have reported a reduced risk of SGA and preterm birth.[3,6-8] In addition, consumption of large amounts of alcohol during pregnancy is associated with occurrence of fetal malformations,[9] mental retardation[4] and behavioral and psychosocial disorders during childhood and adolescence.[10,11]

LBW is a source of concern within healthcare because it is associated with higher neonatal and infant morbidity and mortality. Also, it is a heterogeneous condition because of two adverse conditions, i.e. prematurity and intrauterine growth restriction (IUGR), which may act to varying degrees either separately or synergistically.[12,13]

It has been reported that 20% to 65% of women consume alcohol at some time during pregnancy and that 5% to 10% consume levels sufficient to pose a risk to the fetus.[14] There are also significant differences regarding the effects of maternal consumption of alcoholic drinks on fetal outcomes, according to the gestational period during exposure occurred, thus indicating the existence of critical periods, even for low levels of alcohol consumption.[3] However, there is no difference in the level of risk among the different types of drinks (beer, wine and spirits).[15]

OBJECTIVE

The objectives of the present study were to describe alcohol consumption during pregnancy and to assess its association with adverse perinatal outcomes (LBW, SGA and preterm birth) in a Brazilian birth cohort.

METHODS

This nested cohort study formed part of a more extensive observational prospective study in which the main objective was to assess new risk factors for preterm birth and perinatal indicators and their impact on fetal and infant growth in two cohorts in the cities of Ribeirão Preto, São Paulo, and São Luís, Maranhão.[16]

The data used in the present study were from pregnant women who were evaluated during prenatal follow-up only in Ribeirão Preto and were reinterviewed at the time of their children's births. Women were recruited at hospitals and healthcare units on the occasion of a prenatal visit during the first trimester of pregnancy, provided that an ultrasound examination performed up to the 20th week of gestation was available in order to define gestational age. After being informed about the objectives of the study, the pregnant women were invited to the University Hospital of Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), in order to participate in the study after giving their written informed consent. This evaluation was performed during the second trimester of pregnancy, at a gestational age of 20 to 25 weeks involving only singletons. A standardized questionnaire was applied to gather information on identification, reproductive health, maternal lifestyle habits such as alcohol consumption, and demographic and social characteristics. A standardized questionnaire was also applied to these women on the occasion of their childbirth, and anthropometric measurements on the newborn (weight, length and head circumference) were obtained through the medical records. Data gathering was started in January 2010 and ended in July 2011.

The primary outcomes were: i) LBW (birth weight < 2500 g); ii) relationship between birth weight and gestational age (GA), which was classified as SGA when the birth weight was below the 10th percentile of the Williams curve of birth weight for GA;[17] adequate for gestational age (AGA) when the birth weight was between the 10th and 90th percentiles; and large for gestational age (LGA) when the birth weight was above the 90th percentile of the same curve; and iii) newborns with a GA of less than 37 completed weeks were classified as preterm.

The independent variable was alcohol consumption during pregnancy. The women were asked to report the frequency (as days per week), the amount (as number and type of glasses), the type of alcoholic drink consumed (beer, wine or spirits such as whisky, gin, vodka or rum) and the period of gestation during which alcohol intake occurred (first, second or third trimester). The amount of each drink consumed, in ml, was then calculated. This value was then converted to grams of absolute alcohol (alcohol density), taking into account the percentage of absolute alcohol present in each drink (5% absolute alcohol in beer, 12% in wine and 40% in spirits). When present, the maternal consumption of alcoholic beverages was classified as low (1 g to 20 g of absolute alcohol per day), moderate (21 g to 40 g of absolute alcohol per day) or high (41 g or more of absolute alcohol per day),[18] and perinatal outcomes according to these levels of alcohol were calculated. For non-adjusted and adjusted analyses, alcohol consumption was transformed into a dichotomous variable (yes/no) because of the small number of moderate and high drinkers.[5]

The potential confounding variables included were maternal age (years), mother's skin color (white or other), maternal schooling (completed years), marital status (with or without a partner), family head's occupation (non-manual, skilled manual, semiskilled manual, unskilled manual or not within the economically active population),[19] body mass index (BMI, kg/m^2), maternal smoking during pregnancy and gestational hypertension.

The sample size was originally calculated by considering a 12% prematurity rate and a 10% error, with the significance level set at 0.05.[16] A total of 1,400 women were included, but only 1,370

were assessed at two time points, i.e. in the second trimester of pregnancy and at delivery. However, using an estimate of alcohol consumption among Brazilian pregnant women of approximately 20%,[18] with an odds ratio of 1.80, a type I error (α) of 0.05 and a type II error (β) of 0.20, 1,152 pregnant women would be necessary (768 unexposed and 384 exposed). A flow diagram of our study population is presented in **Figure 1**.

The descriptive statistics included the mean, median, proportion, standard deviation (SD), 95% confidence interval (CI) and interquartile range (IQR). Student's t-test, analysis of variance (ANOVA) and the chi-square test were used to compare means and categorical variables.

Non-adjusted and adjusted logistic regression analyses were calculated to estimate the odds ratio (OR) and 95% CI, in order to express the associations of LBW, SGA and preterm birth with maternal alcohol consumption (yes/no, taking non-consumers as the reference). The data were controlled for potential confounders: maternal age, pregestational body mass index, maternal schooling, mother's marital status, family head's occupation, smoking during pregnancy and gestational hypertension. The goodness of fit of the logistic models was assessed by means of the Hosmer-Lemeshow test. In the next step, in order to assess unhealthy behavior, the effect of smoking on pregnancy was tested by means of an interaction term, with alcohol in another model. The adjusted population-attributable risk (aPAR), which assesses the proportion of cases that would not occur in a population if alcohol consumption were eliminated, was calculated using aPAR = 100 x (aOR – 1)/aOR + (100/ r) – 1, where *r* is the proportion of the population exposed to alcohol and aOR is the adjusted odds ratio.

Significance was set at $P < 0.05$ and all analyses were carried out using the Stata software, version 12.0 (College Station, Texas, USA).

The study was approved by the Research Ethics Committee of Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo (Protocol nº 11157/2008).

RESULTS

Out of the 1370 women studied, 316 (23.0%; 95% confidence interval, CI: 20.9-25.3) consumed alcohol during pregnancy. Most of them had low intake, and beer was the most frequent type of beverage (**Table 1**).

Only 5.1% of the pregnant women reported drinking throughout pregnancy. Alcohol consumption was 14.8% during the first trimester of pregnancy, with closely similar intake in the second and third trimesters (10.7% and 10.5%, respectively). Total alcohol consumption decreased with the progression of gestation, such that the mean intake was 57.1 ± 14.1 g in the first trimester, 41.6 ± 5.9 g in the second, and 35.9 ± 3.4 g in the third. The median daily alcohol intake during pregnancy among the women who reported drinking during pregnancy was 3.89 g (IQR 8 g).

Pregnant women who consumed spirits were the ones with the highest alcohol intake during pregnancy (mean of 40.7 ± 11 g), whereas those who consumed beer and wine had significantly lower alcohol intake (means of 7.7 ± 2.3 g and 5.3 ± 1.2 g, respectively) ($P < 0.001$).

A significant increase in alcohol consumption was observed with increasing maternal age. Women without a partner, smokers and those with hypertension during pregnancy also consumed alcohol in significant quantities. No difference was observed in relation to the other characteristics. between women who consumed alcohol and those who did not (**Table 2**).

The total prevalence of low birth weight was 7.6% (95% CI: 6.4-9.2), SGA 9.6% (8.2-11.3) and prematurity 9.7% (8.2-11.4). Among the LBW infants, 64.7% were preterm and 49.5% were SGA. Among the preterm infants, 11.2% were SGA.

Table 3 analyzes newborn characteristics according to alcohol consumption during pregnancy. The frequency of LBW almost doubled among mothers consuming alcohol ($P = 0.002$). On the other hand, there was no difference between babies born to mothers consuming alcohol and mothers who did not, in relation to mean gestational age, birth weight, SGA and preterm

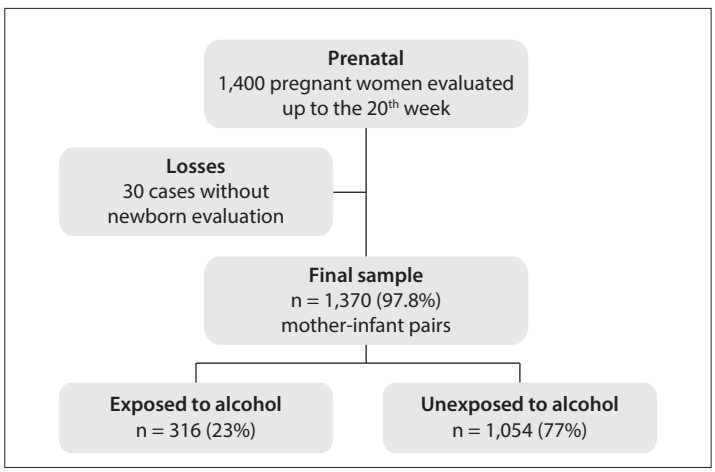

Figure 1. Flowchart of the study population, Ribeirão Preto, 2010.

Table 1. Alcohol consumption during pregnancy (Ribeirão Preto, 2010; n = 1,370)

Alcohol consumption	n	%
Categories of alcohol consumption		
No consumption	1054	76.9
Low (1-20 g/day)	278	20.3
Moderate (21-40 g/day)	24	1.7
High (≥ 41 g/day)	14	1.0
Total consumption	316	23.0
Type of beverage consumed*		
Beer	241	17.6
Wine	114	8.3
Spirits	23	1.6

*Some mothers consumed more than one type of beverage.

birth. Nevertheless, there was some dose-response relationship between alcohol consumption during pregnancy and the risk of low birth weight (6.4% for no consumption, 11.8% for low, 12.5% for moderate and 7.1% for high consumption; P = 0.020).

Table 2. Comparison of maternal and gestational characteristics according to alcohol consumption (Ribeirão Preto, 2010)

Maternal characteristics	Alcohol consumption, n (%)		P
	Yes (n = 316)	No (n = 1054)	
Maternal age (years) (mean, SD)			
< 20	32 (10.1)	160 (15.2)	
20-34	243 (76.9)	797 (75.6)	0.019
≥ 35	41 (13)	97 (9.2)	
Mother's skin color			
White	153 (48.4)	547 (52.5)	0.203
Other	163 (51.6)	495 (47.5)	
Maternal schooling (years) (mean, SD)			
Illiterate	1 (0.3)	1 (0.1)	
Up to 8	97 (30.7)	294 (28)	0.403
9 to 11	188 (59.5)	674 (64)	
≥ 12	30 (9.5)	84 (7.9)	
Marital status			
With a partner	255 (80.7)	914 (86.7)	0.008
Without a partner	61 (19.3)	140 (13.3)	
Family head's occupation			
Non-manual	8 (2.6)	40 (3.9)	
Skilled manual	41 (13.2)	135 (13.2)	
Semiskilled manual	159 (51.3)	534 (52)	0.587
Unskilled manual	102 (32.9)	317 (30.9)	
Not within economically active population	0	4 (0.4)	
BMI (kg/m^2) (mean, SD)	24.7 (4.8)	24.4 (5.3)	0.451
Smoking during pregnancy			
Yes	76 (24.0)	98 (9.3)	< 0.001
No	240 (76.0)	956 (90.7)	
Gestational hypertension			
Yes	55 (17.4)	137 (12.9)	0.048
No	261 (82.6)	917 (87.1)	

BMI = body mass index.

Table 3. Characteristics of the newborns according to maternal alcohol consumption during pregnancy (Ribeirão Preto, 2010)

Characteristics	Alcohol consumption		P
	Yes (n = 316)	No (n = 1054)	
Sex*			
Male	160 (23.7)	513 (76.3)	0.541
Female	156 (22.3)	541 (77.6)	
Gestational age (days)†	272 (16)	273 (14.5)	0.257
Weight (g)†,‡	3,147 (569)	3,208 (544)	0.082
Low birth weight*	37 (11.7)	8 (6.4)	0.002
SGA*	36 (11.4)	96 (9.1)	0.227
Preterm birth*	37 (11.7)	96 (9.1)	0.171

*n (%); †mean (standard deviation); ‡three cases with no information about birth weight; SGA = small for gestational age.

No dose-response relationship was observed for SGA or preterm birth (P = 0.556 and 0.202, respectively).

Unadjusted analysis revealed that alcohol consumption during pregnancy increased the risk of LBW almost twofold (OR 1.91; 95% CI: 1.25-2.92), compared with its absence. After adjustment for confounders, the only perinatal outcome independently associated with alcohol consumption was LBW, although the OR was reduced to 1.62 (P = 0.034) (**Table 4**). The goodness of fit of the models was satisfactory, and the Hosmer-Lemeshow tests were nonsignificant (LBW = 0.894, SGA = 0.646 and prematurity = 0.656).

The effects of smoking and alcohol consumption during pregnancy on neonatal outcomes were explored through interaction, and this revealed high adjusted risks of LBW (OR 3.65; 95% CI: 1.84-7.24; P < 0.001), SGA (2.56; 1.33-4.92; P = 0.005) and preterm birth (2.57; 1.35-4.89; P = 0.004) among women who simultaneously smoked and consumed alcohol, compared with those who did not smoke or drink.

The adjusted population-attributable risk of alcohol consumption was 12.5% for LBW, 3.1% for SGA and 3.5% for preterm birth.

DISCUSSION

In the present study, 23% of the pregnant women consumed alcohol during pregnancy, most of them in a mild manner. A significant almost twofold increase in the risk of LBW was detected among these women, compared with those who never drank.

Internationally, the prevalence of alcohol consumption during pregnancy ranges from 30 to 70%.[20,21] A study in Rio de Janeiro[22] detected prevalence of 7.3% to 26.1%, depending on the screening method adopted, compared with 23% in the present study.

The relationship between alcohol consumption during pregnancy and adverse perinatal outcomes is a matter of controversy. A study conducted in Rio de Janeiro detected no relationship between alcohol consumption and preterm birth, LBW or negative effects on the newborn. However, this lack of association may

Table 4. Unadjusted and adjusted risks according to sociodemographic characteristics and clinical conditions for different perinatal outcomes associated with alcohol consumption during pregnancy (Ribeirão Preto, 2010)

Perinatal outcomes	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*†
LBW	1.91 (1.25-2.92)	1.62 (1.03-2.54)
SGA	1.28 (0.85-1.92)	1.14 (0.74-1.76)
Preterm birth	1.32 (0.88-1.97)	1.16 (0.75-1.78)

*reference: did not consume alcohol; †adjusted for maternal age, pregestational BMI, maternal schooling, marital status of the mother, occupation of the family head, smoking during pregnancy and gestational hypertension; OR = odds ratio; LBW = low birth weight; SGA = small for gestational age.

have been due to the small sample size and to the limited information obtained about dose and frequency of consumption.[23]

A systematic review of low or moderate alcohol consumption did not showed any significant effects on the pregnancy outcomes considered (abortion, stillbirth, fetal growth restriction, preterm, SGA or malformations, including fetal alcoholic syndrome), although it should be pointed out that many of the studies reviewed had methodological deficiencies.[8]

In another systematic review, light to moderate alcohol consumption during pregnancy was not associated with preterm birth or SGA risks.[4]

About 12% of low birth weight cases may be attributed to alcohol consumption, but the aPAR of the present study was lower for SGA and PT and even lower than the levels reported by O'Leary et al.,[2] considering that the latter included frequent drinkers and women who consumed alcohol up to the first trimester of pregnancy. Consequently, prevention of alcohol consumption before the beginning of pregnancy could minimize adverse perinatal outcomes and reduce healthcare budgets.

There are several possible explanations for the failure to detect an association between alcohol and occurrences of SGA and preterm birth. Although maternal characteristics and medical complications were included in the adjusted model, there may have been specific health conditions predisposing towards SGA or preterm birth that we were unable to investigate in the present study (e.g. previous spontaneous preterm labor, placental insufficiency, intrauterine infection and interactions between genetic and environmental factors). Another possible explanation could be the inhibitory effect of alcohol on uterine contractions: this reduces the release of vasopressin and oxytocin during labor[24] and consequently delays the onset of labor.

Henderson et al.[8] suggested that low amounts of alcohol seem to have a small protective effect on birth weight, but no effect on or any reduction of the risk of prematurity, with consumption of up to 72 g of alcohol per week. The authors proposed that one possible explanation for this finding might be a "healthy drinker effect", whereby women with a poorer obstetric history or prognosis are more likely to abstain from alcohol consumption during pregnancy.

The physiopathology of how alcohol may induce low fetal weight may be related to prostaglandins, which play an important role regarding fetal development and birth. Animal models have demonstrated that alcohol increases the production of prostaglandins, including those of the E series. Prostaglandins increase cAMP activity, thus reducing cell division, and an association between high cAMP levels and LBW has been reported. In human beings, increased secretion of prostaglandins and thromboxanes has been detected among alcoholics and their descendants.[6]

In addition, the effects of alcohol consumption depend on its absorption and on mother and fetus metabolism,[25] a circumstance that may be partly genetically determined. Finally, differences may also have been due to the polymorphisms linked to alcohol metabolism, which may vary between populations.[15] Thus, the effects of alcohol consumption need to be further studied in specific subgroups of women.

Alcoholism during pregnancy may be underdiagnosed due to "feelings of guilt" among women who, in order to avoid possible disapproval and reprimands from society and from healthcare professionals, may report lower consumption or deny it, i.e. they may exhibit recall bias.[26] Furthermore, it is possible that women who report ceasing to drink during pregnancy actually did not do so. In the present study, this bias was minimized by using questionnaires applied at two different times (during pregnancy and postnatally). This method is used in order to improve the validity[27] and accuracy[28] of determinations of alcohol exposure.

There are various methods for assessing alcohol consumption, such as analysis of biomarkers in blood, direct interviews and filling out questionnaires. Since these biomarkers and ethanol metabolites are removed relatively rapidly from the bloodstream, they are poor indicators of exposure to alcohol, especially in populations that have low to moderate intake of this substance, as was the case in the present study. Thus, data obtained through interview are the most reliable way to assess mild and moderate levels of alcoholic beverage consumption.[3]

Another difficulty is that alcohol consumption is typically measured through the mean number of drinks per week or month. However, this may mask exposure to peak blood levels of alcohol (caused by binge drinking) and the exact timing of the exposure.[29] In the present population, mild consumption was the most frequent finding (87.9% of the women who drank), but the potential risk to the fetus needs greater depth of investigation. The possible explanations for the lack of concordance between the findings from the various studies include low statistical power to detect small effects and inappropriate characterization of patterns and timing of alcohol consumption.

Smoking, which is an indicator of unhealthy behavior, has been reported to be a modifier of the effect of alcohol consumption on infant birth weight.[30,31] The present results showed significant interaction between alcohol consumption and smoking with regard to the risk of LBW, SGA and preterm birth. Smoking and stress may create a biological environment in which alcohol has more adverse effects due to interactive mechanisms. Several biochemical interactions caused by alcohol and tobacco, with vitamins, folates and other antioxidants, may affect fetal growth during pregnancy.[3,31] In addition, the vasoconstriction of the placenta-umbilical cord unit due to alcohol and tobacco consumption reduces the rate of alcohol elimination from the fetal compartment.[25]

Several limitations of the present study need to be mentioned. Firstly, it should be noted that the sample size was originally not

computed for alcohol consumption,[16] and therefore a type 1 error cannot be ruled out. However, we think that the minimal differences between the estimated and observed sample size would not modify the results. Secondly, alcohol intake during pregnancy was measured on a self-reported basis, which is known to underestimate the frequency and quantity of alcohol consumed by pregnant women. Thirdly, selective participation may have occurred, given that the women who consumed alcohol during pregnancy were in a less healthy condition (**Table 2**) and probably had a higher frequency of non-response regarding high alcohol intake. This may have contributed towards the lack of evidence of any adverse effect from alcohol intake on SGA or preterm birth.[32-34] Finally, because the women were asked about their alcohol intake at 20-25 weeks of pregnancy, some recall bias regarding alcohol intake during the first trimester of pregnancy is possible.

The strength of the present study was that it assessed a birth cohort that had been followed up since the prenatal period, with a high response rate. Since data were collected at two time points, we were able to confirm the information and to adjust it for a wide range of known confounders, such as maternal behavior and sociodemographic factors. Another contribution was that smoking during pregnancy was included in this study. This is a major confounding factor regarding the relationship between maternal alcohol consumption and adverse perinatal outcomes.

CONCLUSIONS

The results reported here indicate that alcohol consumption gave rise to increased risk of low birth weight, but no risk of SGA or preterm birth among the infants born to these mothers. We observed higher risk of low birth weight, SGA and preterm birth among infants born to mothers who smoked in addition to consuming alcohol during pregnancy. The combined effect of smoking and alcohol needs to be taken into account when counseling women about healthy behavior before and during pregnancy.

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This study was presented at the 15th Meeting of Pediatric Research, Jujuy, Argentina, 2013

Source of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), protocol number: 2008/53593-0
Conflict of interests: None

Date of first submission: October 7, 2015
Last received: October 29, 2015
Accepted: November 2, 2015

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Impact of health research on advances in knowledge, research capacity-building and evidence-informed policies: a case study on maternal mortality and morbidity in Brazil

Impacto da pesquisa em saúde nos avanços de conhecimento, construção de capacidades de pesquisa e políticas informadas por evidências: um estudo de caso sobre a morbimortalidade materna no Brasil

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KEY WORDS:
Health services research.
Maternal mortality.
Women's health.
Maternal health services.
Research policy evaluation.

PALAVRAS-CHAVE:
Pesquisa sobre serviços de saúde.
Mortalidade materna.
Saúde da mulher.
Serviços de saúde materna.
Avaliação de políticas de pesquisa.

ABSTRACT

CONTEXT AND OBJECTIVE: National health research systems aim to generate high-quality knowledge so as to maintain and promote the population's health. This study aimed to analyze the impact of maternal mortality/morbidity research funded by the Brazilian Ministry of Health and institutional partners, on the dimensions: **advancing in knowledge, research capacity-building** and **informing decision-making**, within the framework of the Canadian Academy of Health Sciences.

DESIGN AND SETTING: Descriptive study based on secondary data, conducted at a public university.

METHODS: The **advancing in knowledge** dimension was estimated from the principal investigators' publication counts and h-index. Data on **research capacity-building** were obtained from the Ministry of Health's information system. The **informing decision-making** dimension was analyzed from citations in Stork Network **(Rede Cegonha)** documents.

RESULTS: Between 2002 and 2010, R$ 21.6 million were invested in 128 maternal mortality/morbidity projects. Over this period, the principal investigators published 174 articles, resulting in an h-index of 35, thus showing progress in the **advancing in knowledge** dimension. Within the **research capacity-building** dimension, training of 71 students (undergraduate/postgraduate) was observed. Progress in the **informing decision-making** dimension was modest: 73.5% of the 117 citations in the Stork Network documents were institutional documents and norms. One of the projects funded, the 2006/7 National Demography and Health Survey, was cited in program documents.

CONCLUSION: Impacts were shown in the **advancing in knowledge** and **research capacity-building** dimensions. The health research system needs to incorporate research for evidence-informed policies.

RESUMO

CONTEXTO E OBJETIVO: Sistemas nacionais de pesquisa em saúde buscam gerar conhecimentos de qualidade para manter e promover a saúde da população. Este estudo visou analisar o impacto das pesquisas sobre morbimortalidade materna financiadas pelo Ministério de Saúde do Brasil e instituições parceiras, nas dimensões: **avanços no conhecimento, construção de capacidade de pesquisa** e **tomada de decisão informada**, da matriz da Canadian Academy of Health Sciences.

DESENHO DO ESTUDO E LOCAL: Estudo descritivo baseado em dados secundários, realizado em universidade pública.

MÉTODOS: A dimensão **avanços no conhecimento** foi estimada pelas publicações dos coordenadores de pesquisa e índice h. Dados sobre a **capacidade de pesquisa** foram obtidos no sistema de informação do Ministério da Saúde. A dimensão **tomada de decisão informada** foi analisada pelas citações nos documentos da Rede Cegonha.

RESULTADOS: Foram investidos R$ 21,6 milhões de reais em 128 pesquisas sobre morbimortalidade materna entre 2002 e 2010. Nesse período, os coordenadores das pesquisas publicaram 174 artigos, resultando no índice h de 35, mostrando progressos na dimensão **avanços no conhecimento**. Na dimensão **capacidade de pesquisa**, foi constatado o treinamento de 71 estudantes (graduação e pós-graduação). Na dimensão **tomada de decisão informada**, o progresso foi modesto: 73,5% das 117 citações nos documentos da Rede Cegonha eram documentos institucionais e normas. Um dos projetos financiados, Pesquisa Nacional de Demografia e Saúde 2006/7, foi citado em documentos programáticos.

CONCLUSÃO: Impactos foram demonstrados nas dimensões **avanços no conhecimento** e **capacidade de pesquisa.** O sistema de pesquisa em saúde necessita da incorporação de pesquisas para políticas informadas por evidências.

INTRODUCTION

The national health research system has progressively strengthened in Brazil, mainly due to significant government funding of research projects and programs, along with human and institutional capacity-building. The increase in Brazilian scientific production is one of the advances resulting from these investments.[1,2] In 2003, the process of setting the health research priorities agenda started with involvement of different social players (researchers; healthcare sector, education and science and technology decision-makers; healthcare system users; healthcare worker organizations; professional associations; and representatives of private companies).[3,4] In 2004, the agenda[5,6] was implemented in accordance with the recently published "good practice principles":[7] inclusive process, information gathering, careful planning and funding policy, transparency and evaluation. The efforts that were made to guide health research policy have achieved and legitimated an unprecedented developmental upsurge in support for strategic health research.[4]

However, some components of the health research system in Brazil, such as use of research results and evaluation of their impact, are poorly structured and developed both by public institutions and agencies and by researchers themselves.[8] Several authors have pointed out that the participatory process in setting research priorities contributes towards identifying the complex needs of the health system and services, and fosters an environment of opportunities for further research built on existing knowledge.[9-13] Thus, on the one hand, this can improve both researchers' ability to provide answers to assist with understanding health determinants and their effects on health equity, and also their ability to develop new and better interventions for preventing and treating diseases in different population groups and social and political contexts. On the other hand, these scholars have pointed out the importance of effective management of agencies and institutions with regard to planning, promotion and implementation of funding mechanisms for efficient and equitable allocation of investment in research programs. According to these authors, the participatory process is one element that favors use and ownership of research results by the social players, with a potential impact on healthcare practices and policies within the healthcare sector and on strengthening the sector's own production and scientific capacity.

Over the past three decades, infant mortality rates have reduced substantially in Brazil, decreasing by 5.5% per annum in the 1980s and 1990s, and 4.4% per annum since 2000, to reach 14.6 deaths per 1000 live births in 2012; neonatal deaths account for 70% of infant deaths. On the other hand, official statistics show that maternal mortality ratios have remained stable over the past 10 years. Substantial challenges remain, including overmedicalization of childbirth (nearly 50% of babies are delivered by means of caesarean section), maternal deaths caused by illegal abortions and high frequency of preterm deliveries.[14,15]

In 2011, the Ministry of Health established the Rede Cegonha (Stork Network), with the aim of expanding access and improving the quality of prenatal care and assistance during delivery, postpartum care and child care for up to 24 months after birth.[16] The initiative was based on the following laws: Law No. 8,080 dated November 19, 1990, which provides for the conditions for promotion, protection and recovery of health within the public healthcare services (SUS); Law No. 11,108 dated April 7, 2005, which guarantees mothers' right to have a companion with them during labor and the immediate postpartum period in SUS hospitals; and Law No. 11,634 dated December 27, 2007, which provides for the right of pregnant women to be linked to the maternity ward, where they will receive care under SUS. Rede Cegonha is a government priority.

The analysis on the impact of research on maternal mortality funded by the Ministry of Health and institutional partners may contribute towards strengthening institutions and funding agencies regarding the understanding of research processes, and towards identifying opportunities, difficulties and challenges relating to achieving the desired impacts from funded research.

OBJECTIVE

This study focuses on the impact of research on maternal mortality funded by the Ministry of Health and institutional partners between 2002 and 2010, as measured by a series of well-established impact indicators.

METHODS

Analytical framework

The framework of the Canadian Academy of Health Sciences (CAHS) has five dimensions that make it possible to identify and evaluate the impact of research.[17] This study focused on three of these: 1) **advancing in knowledge**; 2) **research capacity-building**; and 3) **informing decision-making**. The fourth dimension is **health benefits**, which recognizes progress regarding prevention, diagnosis, treatment, palliative care and progress in relation to health status, social and environmental risk factors, health determinants and changes to healthcare system performance. This, and the fifth dimension, **economic and social benefits**, were not included in the analysis since the data available did not cover the complex indicators of these two dimensions.

The **advancing in knowledge** dimension reveals new health research discoveries and progress, as well as contributions made to the scientific literature. The categories and indicators for this dimension were: (1) **research activity**: publication counts, i.e. the number and percentage of scientific publications and type; and (2) **research quality**: number of peer-reviewed journal articles, percentage of articles published in indexed journals, impact

factor (h-index, is a measurement that aims to describe the scientific productivity and impact of a researcher or journal), and citations received per article (expressed as medians and interquartile intervals).

The **research capacity-building** dimension comprises development/enhancement of individual and team research skills in capacity-building for advances in knowledge. The category and indicator was **research capacities, skills and personnel**: number and percentage of students trained.

The **informing decision-making** dimension shows how research expands its outcomes and influences evidence-based policies. The categories and indicators were: (1) **health-related decision-making**: healthcare protocols, guidelines, manuals and technical norms, and technical methods of clinical evaluation; and (2) **qualitative indicators**: citations in public health policies and programs. The dimensions, categories and indicators were chosen for this study taking the following criteria into consideration: access and availability of data, data validity, reproducibility, cost and relevance.

Data gathering and categories analyzed

Data on research investments over the period 2002-2010 were obtained from the Ministry of Health science and technology managerial information system <http://pesquisasaude.saude.gov.br/bdgdecit/> (accessed on December 10, 2015). For each project included in this study, identification data was collected (name of principal investigator (PI), title, summary, amount invested, year of contract, state/province and region), research capacity-building (number of undergraduate and postgraduate students involved; undergraduate course final dissertations, masters' dissertations and PhD theses concluded) and applicability of research results according to the PI.

Projects were selected using the filter "Women's Health" as the primary or secondary research agenda; this classification of projects into agendas is done by the PI at the time of project submission. The subgroup of projects relating to maternal mortality and morbidity and the type of research approach were classified by two of the authors in a blind and independent manner, based on project titles and summaries; in four cases the summary was missing and those projects were classified based only on the title (none of them were related to maternal mortality).

The type of research approach was classified according to the definition used by the Canadian Academy of Health Sciences (CAHS).[17] CAHS has defined that health services research (HSR) examines how people get access to healthcare, how much care costs and what happens to patients as a result of this care. The main goals of HSR are to identify the most effective ways to organize, manage, finance and deliver high-quality care; reduce medical errors; and improve patient safety.[18] **Population and public health research** (PPHR) is defined as research with the goal of improving population health, or of defined subpopulations, through better understanding of the ways in which social, cultural, environmental, occupational and economic factors determine health status. The ambit of PPHR includes research into the complex interactions (biological, environmental, social and cultural) that determine the health of individuals, communities and global populations.[19]

Clinical research (CR) has "the goal of improving the diagnosis and treatment (including rehabilitation and palliation) of disease and injury; improving health and quality of life of individuals as they pass through normal life stages". **Biomedical research** (BR) is conducted "with the goal of understanding normal and abnormal human functioning at the molecular, cellular, organ system and whole body levels, including development of tools and techniques to be applied for this purpose; developing new therapies or devices that improve health or the quality of life of individuals, up to the point where they are tested on human subjects".[17]

One indicator for the **advancing in knowledge** dimension was "publication counts", i.e., the number and percentage of scientific publications according to the type of research approach. We accessed the list of articles on maternal mortality and morbidity included in the curricula of the PIs funded by the Ministry of Health and partners. All articles published from 2002 to 2010 and informed in the curricula were extracted from the Lattes Platform, which is the major platform for curricula encompassing virtually every Brazilian researcher, using the ScriptLattes software (http://buscatextual.cnpq.br/buscatextual/busca.do). The data were exported to a RIS (Research Information Systems) file and then imported to Mendeley Desktop; duplicated articles were excluded, thus resulting in a total of 2,961 articles. These were then classified according to whether they related to maternal mortality and morbidity, based on the list of selected keywords appearing in the article titles. This resulted in identifying 174 articles on maternal mortality and morbidity. In addition, the number of dissertations and theses developed during the project was calculated according to information provided by the principal investigator in the Ministry of Health S&T information system <http://pesquisasaude.saude.gov.br/bdgdecit/>.

The **research quality** category was assessed according to the number of peer-reviewed journal articles, percentage of articles published in indexed journals, impact factor (h-index) and citations received per article (expressed as medians and interquartile intervals). The Google Scholar database (http://scholar.google.com) was used to obtain the number of citations received by each article, and journals were considered to be indexed when included in Google Scholar metrics. The h-index was calculated based on Google Scholar citations.

With regard to the **research capacity-building** dimension, the number of undergraduate and postgraduate students trained through the projects was calculated according to the information provided by the principal investigator in the abovementioned Ministry of Health science and technology information system.

With regard to the **informing decision-making** dimension, one of the focus area was Rede Cegonha, the government initiative that was launched in 2011 to reduce maternal mortality and morbidity. We analyzed clinical protocols, guidelines and manuals published by the Ministry of Health, which could indicate the use of evidence produced by these projects in the **health-related decision-making category**.[20-24] **Citation in public health policy documents** was also considered, since we investigated Rede Cegonha policy documents.[25-27] We also investigated what the principal investigators pointed out as forms of applicability of research results in the category **"health-related decision-making"**, which they registered in the Ministry of Health S&T information system.

These publications were classified as "grey literature", in accordance with the United Kingdom Department of Health definition: "produced at all levels of government, academia, business and industry in print and electronic formats, but which is not controlled by commercial publishers; it may also be defined, broadly, to include everything except peer-reviewed books and journals".[28]

RESULTS

Between 2002 and 2010, the Ministry of Health and partner institutions funded 128 research projects on maternal mortality and morbidity (**Table 1**). The distribution of maternal mortality and morbidity projects per year showed that 78 proposals (56% of the total) were approved in 2004 and 2007, when two large Calls for Proposals were launched: "Maternal Mortality and Neonatal Morbidity and Mortality"[29] in 2004, and "Women's Health"[30] in 2007.

Regarding the approach, there were 84 projects on Population and Public Health Research (PPHR), which received by far the largest investment (**Table 1**). The investment per project was R$ 217,000 and R$ 83,000 in the first and second project approach, respectively. On average, HSR projects received less than half the investment made in PPHR.

With regard to regional distribution, the institutions receiving funding (mostly public universities and public research institutes) were predominantly located in the northeastern region (38%) and southeastern region (33%). However, in analyzing the amount of investments, the southeast received five times more resources than the northeast (**Figure 1**).

Analysis of the **advancing in knowledge** dimension according to publication counts found 245 publications: 174 scientific articles (**Table 2**) and 71 other types of scientific publications: doctoral theses (16), master's dissertations (41) and undergraduate end-of-course dissertations (14). Articles with a Population and Public Health Research approach predominated. Regarding postgraduate products, the majority of the publications were master's dissertations. Only one patent was deposited.

With regard to research quality, the 174 papers produced had an h-index of 35, and 154 (89%) were published in indexed journals. The median number of citations received by each paper was 9, with an interquartile interval from 3 to 27.75. Articles classified as Population and Public Health Research or as Health Services Research had a higher impact than those in the other two categories (**Table 2**). **Table 3**[31-42] presents the top three most cited articles for each type of research approach. Five out of the 12 examples

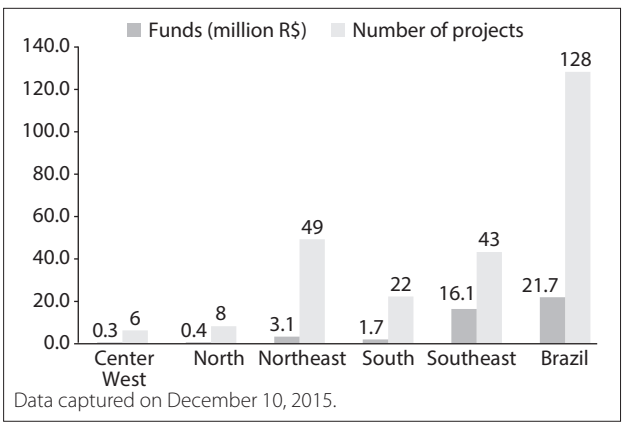

Figure 1. Investments and numbers of projects within maternal mortality and morbidity research funded by the Ministry of Health and partner institutions, according to geographical regions. Brazil, 2002-2010.

Table 1. Research projects on maternal mortality and morbidity funded by the Ministry of Health and its partners, according to type of research approach. Brazil 2002-2010*,†

Type of research approach‡	Number of projects n (%)	Investments, in R$ thousands (%)	Funds invested per project, in R$ thousands
Population and public health research	84 (65.6%)	18,273.3 (84.4%)	217.5
Health services research	30 (23.4%)	2,493.0 (11.5%)	83.1
Biomedical research	13 (10.2%)	854.6 (3.9%)	65.7
Clinical research	1 (0.8%)	35.7 (0.2%)	35.7
Total	128 (100%)	21,656.8 (100%)	169.1

*Partner institutions: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Ministério da Ciência e Tecnologia (MCT), Financiadora de Estudos e Projetos (Finep), Fundações Estaduais de Amparo à Pesquisa (FAPs); †Data captured on December 10, 2015; ‡According to the Canadian Academy for Health Sciences.

resulted from research conducted abroad; clear predominance of international cooperation was found among biomedical and clinical research. However, most of these research results are applicable to all pregnancies, and therefore can be extrapolated to a Brazilian scenario.

The **research capacity-building** dimension was evaluated according to information provided by the principal investigators: 71 undergraduate and postgraduate students trained during the different stages of development of the research.

The **informing decision-making** dimension, focusing on the use made of research results in official protocols, guidelines, manuals and healthcare policy documents published through the recently launched program to reduce maternal mortality (Rede Cegonha), showed poor use made (**Table 4**). The eight official Brazilian Ministry of Health documents were analyzed and 117 citations were compiled. The vast majority (73.5%) could be classified as grey literature. The Demography and Health Survey, which was one of the projects analyzed here, was cited in two Ministry of Health documents.

Sixty-eight researchers (53%) pointed out various forms of applicability of research results in the category **health-related decision-making**. **Table 5** presents a synthesis of the reported applications. Knowledge of risk factors, especially in relation to infectious and hypertensive disorders during pregnancy, formulation of policies and implementation of strategies and actions for improving maternal and newborn health, prevailed as potential

Table 2. Articles published on maternal mortality and morbidity that were included in the curricula of researchers funded by the Brazilian Ministry of Health and its partners, according to type of research approach*,†. Brazil, 2002-2010

Classification of article according to research approach‡	Number of articles (n)	Proportion of articles (%)	h-index	Citations: median (interquartile interval)
Population and Public Health Research	87	50.3	25	11 (4; 29.5)
Health Services Research	43	24.7	18	11 (6; 39)
Biomedical Research	13	7.5	5	4 (1; 6)
Clinical Research	31	17.8	10	4 (1; 12.5)
Total	174	100.0	35	9 (3; 27.8)

*Partner institutions: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Ministério da Ciência e Tecnologia (MCT), Financiadora de Estudos e Projetos (Finep), Fundações Estaduais de Amparo à Pesquisa (FAPs); †Data captured in June 2014; ‡According to the Canadian Academy for Health Sciences.

Table 3. Top three most cited articles published on maternal mortality and morbidity by investigators funded by the Brazilian Ministry of Health and its partners, according to type of research approach. Brazil, 2002-2010

Research approach* and article title	Year	Journal reference	Citations
Population and public health research			
Maternal mortality in Brazilian State Capitals: some characteristics and estimates for and adjustment factor	2004	Rev Bras Epidemiol, 7(4):449-60.[31]	187
Racial, sociodemographic, and prenatal and childbirth care inequalities in Brazil, 1999-2001	2005	Rev Saude Publica, 39(1):100-7.[32]	151
Cesarean sections: who wants them and under what circumstances?	2003	Cad Saude Publica, 19(6):1611-20.[33]	98
Health services research			
Aspects of women's satisfaction with childbirth care in a maternity hospital in Rio de Janeiro	2004	Cad Saude Publica, 20(Sup 1):S52-S62.[34]	124
Quality of birth care in maternity hospitals of Rio de Janeiro, Brazil	2005	Rev Saude Publica, 39(4):646-54.[35]	102
Adequacy of the two references services for women with high risk pregnancies at maternity hospitals of the Brazilian Public Health System in the city of Recife, in the State of Pernambuco	2007	Rev Bras Saúde Matern Infant, 7(3):309-17.[36]	81
Biomedical research			
The pregnancy-induced increase of plasma angiotensin-(1-7) is blunted in gestational diabetes	2007	Regul Pept, 141(1):55-60.[37]	25
Increased serum phosphodiesterase activity in women with pre-eclampsia	2006	Br J Obstet Gynaecol, 113(5):577-9.[38]	17
Increased circulating thrombomodulin levels in pre-eclampsia	2008	Clin Chim Acta, 387(1-2):168-71.[39]	12
Clinical research			
Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized, placebo-controlled trial	2002	Lancet, 359(9321):1877-90.[40]	475
Comparison of Magnesium Sulfate and Nimodipine for the Prevention of Eclampsia	2003	N Engl J Med, 348(4):304–11.[41]	233
Beneficial interventions for maternal mortality prevention in the prenatal period	2006	Rev Bras Ginecol Obstet, 28(5):310-5.[42]	71

*According to the Canadian Academy for Health Sciences.

Table 4. Citation of scientific evidence in the official protocols, guidelines, manuals and health policy documents published by the Ministry of Health for Rede Cegonha ("Stork Network"). Brazil 2011-2013*

Classification according to type of publication cited	Number of citations*	Proportion of citations (%)
Published institutional documents: from the Ministries of Health, Labor and Social Development and from international organizations: UNDP and PAHO	52	44.4
Scientific references: scientific books and journal articles; master's dissertations†	28	23.9
Legislative norms: laws, norms, resolutions and directives	23	19.7
Internal institutional documents	11	9.4
Congress abstracts	3	2.6
Total number of documents cited	117	100.0

*All the eight official Rede Cegonha documents were analyzed, totaling 117 citations; †18 books published in Brazil, 5 books published abroad, three articles published in Brazil; two master's dissertations.
UNDP = United Nations Development Programme; PAHO = Pan-American Health Organization.

Table 5. Perspective of the principal investigators of research projects financed by the Ministry of Health and partners, regarding the applicability of research results within the informed decision-making dimension. Brazil, 2002-2010

Analytical categories of the applicability of research results*	n	%
Potential use of research findings	60	88.2
Knowledge about social and biological determinants and risk factors	36	52.9
Formulation and implementation of policies, strategies and actions	30	44.1
Improvements in obstetric and neonatal care	18	26.5
Planning, organization and evaluation of services	8	11.8
Information for future research	3	4.4
Identification and treatment of maternal complications during pregnancy	1	1.5
Real use of research findings	12	17.6
Use of technology	10	14.7
Training of healthcare professionals	5	7.4
New knowledge of risk factors and social inequalities	2	2.9
Changes induced by search results	3	4.4
Information for users	3	4.4
Impact on clinical practice	1	1.5
Potential users of search results	47	69.1
Clinical decision managers and healthcare professionals	33	48.5
Policy makers and healthcare managers	23	33.8
Social organizations	3	4.4
Academic investigators	2	2.9
Legislators	1	1.5
Dissemination of research results	9	13.2
Training of healthcare professionals	6	8.8
Dissemination of results among healthcare workers	4	5.9
Coordination with the healthcare sector to implement policies	1	1.5
Changes in legislation to protect women	1	1.5

*Multiple answers allowed.

evidence of use of research results. Healthcare service managers and healthcare workers were cited as potential users of research results. However, few changes to healthcare services were cited by the principal investigators, regarding the real use of the evidence produced.

DISCUSSION

The aim of this study was to analyze the contributions made by the investments and the incorporation of research findings regarding maternal mortality and morbidity in public health policy formulation in Brazil. This analysis was conducted based on three analytical dimensions of the CAHS framework, with emphasis on citations of articles, dissertations and theses in preparing the official Rede Cegonha public policy documents. This public policy was formulated in the form of a care network "to ensure women's right to reproductive planning and humanization of the pregnancy, childbirth and postpartum periods, as well as the child's right to safe birth and healthy growth and development".[16]

The predominance of institutional documents and legislative norms among the citations of official publications reflects policymakers' practice of prioritizing existing technical and legislative regulations to guide health managers primarily with regard to organization, functioning and physical restructuring of the healthcare network, including intensive care units, provision of obstetric and neonatal care and transfer of funds. The scarce use of scientific references reaffirms the difficulty in incorporating knowledge to promote improvements in healthcare systems that have been pointed out in several studies.[43-46] However, it also reveals the challenge of measuring the influence of research findings on decision-making, because of the inherent dynamics of the political process in healthcare management.[47,48]

At the same time, this poses questions regarding the ability of researchers to provide answers that will enable interventions that promote significant changes towards safe motherhood, improve professionals' technical quality and clinical practices and enhance system performance and healthcare programs.[45,46]

However, in order for researchers to meet this demand, supportive environments are needed, so that on the one hand, researchers can be brought closer to the needs of healthcare services and, on the other hand, substantial investment in HSR can be made by public institutions and agencies, thereby promoting the participation of healthcare institutions.[13,17] As pointed out earlier, although HSR accounted for 23.0% of the projects funded, this represented only 11.5% of the total amount of investments.

Strengthening of the national health research system requires efforts to understand the needs of the players in the system and, in particular, strategies to promote translation and communication of research results, so as to inform policy and healthcare

practices. The traditional forms of dissemination of research results among scientists are not adequate, and innovative ways are needed in order to foster access to the results and recommendations for the healthcare system.

Another point to be highlighted concerns the distribution of research funds in Brazil. In general, larger investments are targeted to areas with the best science and technology capabilities. As our results demonstrated, the southeastern region, which has better-structured science and technology capacities, received five times more resources, despite the fact that there were more projects in the northeastern region. However, the Brazilian health research system needs to achieve a balance between the distribution of funds according to science and technology capacity, while also taking into account local health situations and priorities. In the case of maternal mortality, there are profound regional, ethnic and socioeconomic disparities: higher maternal mortality levels affect the population in the poorer northern and northeastern regions, compared with the more affluent southern and southeastern regions.[15] Research investments could promote equity through projects to investigate better access to healthcare, organization of care processes and ways of improving clinical practice and women's safety during the prenatal, childbirth and postpartum periods.[14,49] These subjects could be studied by research institutions in the regions most affected, through networking with the more traditional and consolidated science and technology institutions.

There is some evidence that investigators in the northeastern region respond very well to research funds allocated there. The scientific publications resulting from the Research for SUS Program (PPSUS) over the period 2004-2009 comprised 1,020 master's dissertations and doctoral theses. The northeastern region reported the largest number of academic degrees: 322 master's and doctoral degrees (32%), i.e. ahead of the more developed and populated southeastern region.[4]

The Brazilian health research system therefore needs to strengthen research functions, such as monitoring of funding distribution mechanisms, development of human and physical capacity to conduct, absorb and use research, and evaluation of the impacts of research. One noteworthy issue is the challenge of promoting a culture that encourages involvement of investigators in policy and decision-making while, on the other hand, facilitating interaction between researchers and policymakers, service managers, providers, healthcare workers and service users.[50] One proposal is to increase investments and strategies for HSR through participation of healthcare service managers, workers and users in formulating and implementing research and incorporating its results.

The EVIPNet Brazil initiative can be highlighted. This was started in 2009 and is run by the Ministry of Health and the Pan-American Health Organization (PAHO). Its objective is to establish mechanisms to facilitate the use of relevant scientific evidence in formulating and implementing health policies (http://brasil.evipnet.org/).

The investigators funded by the Ministry of Health and partners produced a reasonable number of high-quality papers, as showed by an h-index of 35 and the observation that nearly 90% of the articles were published in indexed journals. This is an indication that research projects on maternal mortality and morbidity generated important scientific results and can be used as an important means of measuring funding efficiency. Articles classified as Population and Public Health Research (h-index of 25) or as Health Services Research (h-index of 18) had higher impacts, with higher medians for citations received and also a much higher top quartile. We can infer that Brazilian researchers who developed Population and Public Health Research relating to maternal mortality and morbidity tended to produce articles with higher citation indexes than those dedicated to the Biomedical field. However, Clinical Research accounted for the top two most cited articles.

There are some limitations to consider in relation to using article output as a funding success indicator. Some research projects may result in articles published years later, and therefore not included in our analysis. It is hard to determine a reasonable time interval for funded research to generate publications. Nonetheless, it should be noted that research that is more complex or takes longer to conduct might generate published papers with higher impact on a future date. This is primarily because different types of research will have different timetables: an *in vitro* study will most likely produce faster results and publication than a cohort study or health services research. Moreover, some research may gather additional funding to expand its objectives, methodology or sampling, thus delaying publication but also producing more relevant information. In this way, some papers receive support from more than one institution, while rarely mentioning the real contribution of each source of funding.

The publications list for each author was extracted from the Lattes Platform, which is an extremely reliable but self-informed mechanism, and which might result in underreporting to some extent. The classification of research approach using only the title was a limiting factor. Despite those limitations, the number and quality of publications are considered to be good ways of measuring research impact.

With regard to the **informing decision-making** dimension, we used most of the indicators suggested by the Canadian Framework, such as citation of research results in clinical protocols, guidelines and manuals published by the Ministry of Health for policy, programs or healthcare. However other indicators could be used, such as citation of research results for capacity-building and training of healthcare professionals, and in the media (newspaper articles and interviews in the press); this constitutes a study limitation.

CONCLUSION

Impacts were shown with regard to the **advancing in knowledge** and **research capacity-building** dimensions. However, the Brazilian national health research system needs strengthened mechanisms for informing evidence-based policies and promoting incorporation and use of research results into policy formulation, strategies and actions, in order to improve maternal and newborn healthcare services. Recognition of the relevance of health research investments is strengthened insofar as it can be shown to produce impacts on policy, and this requires engagement of researchers for effective interaction with various sectors of society, and in particular healthcare policy stakeholders.

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Conflicts of interest: None
Sources of funding: None

Date of first submission: July 24, 2015
Last received: October 29, 2015
Accepted: November 2, 2015

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Prevalence of high blood pressure measured in the Brazilian population, National Health Survey, 2013

Prevalência da hipertensão arterial aferida na população brasileira, Pesquisa Nacional de Saúde, 2013

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KEY WORDS:
Hypertension.
Health surveys.
Risk factors.
Chronic disease.
Cardiovascular disease.

PALAVRAS-CHAVE:
Hipertensão.
Inquéritos epidemiológicos.
Fatores de risco.
Doença crônica.
Doenças cardiovasculares.

ABSTRACT

CONTEXT AND OBJECTIVE: High blood pressure (hypertension) is the most frequent cause of morbidity and a major risk factor for cardiovascular complications. The aim here was to describe the prevalence of blood pressure greater than or equal to 140/90 mmHg in the adult Brazilian population and federal states, along with self-reported information about previous medical diagnoses of hypertension, use of medication and medical care for hypertension control.

DESIGN AND SETTING: Cross-sectional study analyzing information from the National Health Survey of 2013, relating to Brazil and its federal states.

METHODS: The sample size was estimated as 81,254 households and information was collected from 64,348 households. The survey consisted of interviews, physical and laboratory measurements. Systolic blood pressure was considered to be high when it was ≥ 140 mmHg and diastolic blood pressure, ≥ 90 mmHg.

RESULTS: It was found that 22.8% of the population has blood pressure measurements ≥ 140/90 mmHg. The proportion was higher among men than among women: 25.8% versus 20.0%. The frequency increased with age, reaching 47.1% in individuals over 75 years and was highest in the southeast and south. 43.2% reported previous medical diagnoses of hypertension and, of these, 81.4% reported using medication for hypertension and 69.6%, going to the doctor within the past year for pressure monitoring, thus showing regular medical follow-up.

CONCLUSION: These results are important for supporting measures for preventing and treating hypertension in Brazil, with the aim of achieving the World Health Organization's goal of reducing hypertension by 25% over the next decade.

RESUMO

CONTEXTO E OBJETIVO: Pressão alta (hipertensão) é a causa mais frequente de morbidade e importante fator de risco para complicações cardiovasculares. O objetivo foi descrever a prevalência de pressão arterial maior e igual a 140/90 mmHg na população adulta brasileira e nas Unidades Federadas, bem como informações autorreferidas sobre diagnóstico médico prévio de hipertensão, uso de medicação e acompanhamento médico para controle de hipertensão arterial.

TIPO DE ESTUDO E LOCAL: Estudo transversal, analisando informações da Pesquisa Nacional de Saúde em 2013, referentes ao Brasil e Unidades Federadas.

MÉTODOS: A amostra foi estimada em 81.254 domicílios e foram coletadas informações em 64.348 unidades domiciliares. A PNS consistiu em entrevistas, medidas físicas e laboratoriais. A pressão arterial foi considerada elevada quando a sistólica aferida ≥ 140 mmHg ou a pressão arterial diastólica ≥ 90 mmHg.

RESULTADOS: Foi identificado que 22,8% da população tem pressão arterial medida ≥ 140/90 mmHg, sendo mais elevada em homens 25,8%, e 20,0% em mulheres. A frequência aumenta com a idade, chegando a 47,1% acima de 75 anos e as medidas foram mais elevadas nas regiões Sudeste e Sul; 43,2% referiram diagnóstico médico prévio de hipertensão; destes, 81,4%, relataram usar medicação para hipertensão e 69,6% foram ao médico no último ano para monitoramento da hipertensão, mostrando acompanhamento médico regular.

CONCLUSÃO: Estes resultados são importantes para apoiar medidas de prevenção e tratamento ao hipertenso no país, visando atingir a meta da Organização Mundial de Saúde de redução da hipertensão em 25% na próxima década.

INTRODUCTION

High blood pressure is the most frequent cause of morbidity and is the main risk factor for cardiovascular complications such as stroke, acute myocardial infarction, chronic kidney disease and vascular diseases, among others.[1,2] It is one of the causes of decreased quality of life and life expectancy and leads to high socioeconomic costs, thereby directly affecting individuals, families, the healthcare system and the economy.[2,3]

The World Health Organization (WHO) has estimated that approximately 25% of the world population has high blood pressure, and growth of 60% in the numbers of cases of this disease by 2025 has been predicted.[1,2] In Brazil, cardiovascular diseases are responsible for 30% of deaths with known causes, and are also the biggest cause of hospitalization in the Brazilian National Health System (SUS).[4,5]

Because of operational difficulties and the high cost of measuring high blood pressure in the field, studies using self-reported data have been used as a proxy for these measurements.[6,7] In Brazil, health surveillance done by means of telephone interviews (VIGITEL surveys) have indicated that the overall prevalence of high blood pressure is 24.8%, and that the prevalence increases with age, such that more than half the population over the age of 55 years is affected.[8]

Population-based prevalence studies on blood pressure measurements in Brazil are still scarce. Most of them are limited to institutions or municipalities, without national scope. Different methodological approaches have been used, along with different samples, different population groups (sex, age, income and educational level) and different diagnostic criteria, without any standardization when measuring blood pressure, which makes comparisons difficult.[3,9]

A review study that used blood pressure of 140/90 mmHg as a cutoff indicated prevalence of around 20%, without distinction between the sexes, but with an evident tendency towards increasing pressure with age.[3] In Brazil, population-based studies have revealed that between 37% and 67% of patients with high blood pressure are treated, but that blood pressure control is low among these treated patients, reaching levels of only 20% to 26%.[9]

The Longitudinal Study of Adult Health (Estudo Longitudinal de Saúde do Adulto, ELSA-Brasil) used a cohort composed of teachers and other employees at six Brazilian universities aged between 35 and 74 years. The study demonstrated that 35.8% of the participants met the predefined criteria for hypertension, which were systolic/diastolic blood pressure greater than or equal to 140/90 mmHg or use of medication prescribed for high blood pressure. Moreover, among the individuals with high blood pressure, 80% were aware that they presented high blood pressure, 78% were undergoing treatment and 56% presented controlled levels.[10,11]

In 2013, the National Health Survey (Pesquisa Nacional de Saúde, PNS) included blood pressure measurement among adults, along with questions about high blood pressure diagnosed by doctors, the care provided and use of medications, among other topics.[12,13] The present study is the first to analyze the high blood pressure data measured through the PNS in Brazil.

OBJECTIVE

The objective of this study was to describe the prevalence of high blood pressure above 140/90 mmHg among the adult Brazilian population and within each federal state, along with self-reported information about previous medical diagnoses of hypertension, use of medication and medical follow-up for high blood pressure control.

METHODS

This was a cross-sectional study carried out using secondary data from the PNS, which was a population-based survey conducted by the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE) in 2013, in partnership with the Brazilian Ministry of Health.[12,13] The survey was household-based and the sample that was used was grouped in three stages (cluster sampling), with stratification of the primary sampling unit (PSUs). Census tracts or sets of census tracts formed the PSUs, households were the second-stage units and inhabitants aged 18 years or over were the third-stage units. The subsample of PSUs was selected through simple random sampling.

The sample size was estimated in the PNS as 81,357 households, and information was collected from 64,348 of them. Taking into account closed households, the loss rate was 20.8% and the no-response rate was 8.1%.[12,13] A total of 60,202 people participated in the individual interviews. Among these, 59,402 people had their blood pressure measured, of whom 25,920 were men and 33,482 were women. This was the first national survey on blood pressure levels among adults aged 18 years or over. High blood pressure was taken to be a systolic blood pressure measurement of greater than or equal to 140 mmHg or a diastolic measurement of greater than or equal to 90 mmHg.[14]

Blood pressure was measured by a trained team using a calibrated digital device. The individuals needed to be at rest and were instructed to empty their bladders, not to smoke or drink during the 30-minute period preceding the measurement and not to do any physical activities during the one-hour period preceding the measurement. The blood pressure measurements were made with the individual in a seated position, having rested for at least five minutes beforehand. The subjects were instructed to keep their back relaxed and supported against the backrest of the chair, not to cross their legs and to leave their left arm free of

clothing and resting on a table at the same level as their chest or heart. Three blood pressure measurements were made, with two-minute intervals between them. The measurements were then inserted into a smartphone. The average between the second and third measurements was used for the present study.[14]

A controlled imputation process was used in relation to situations that were deemed to be no-response situations. A set of integrated computational routines were used within a system named CIDAQ (Crítica e Imputação de Dados Quantitativos, i.e. Criticism and Imputation of Quantitative Data). This takes into consideration the combined behavior of all the variables recorded: age, sex, weight, height and family per-capita income. More details can be seen in other published materials.[12,14]

The present study describes the prevalence of individuals with blood pressure ≥ 140/90 mmHg in the Brazilian adult population, according to sex, age group, region of the country and federal state, with the 95% confidence interval (CI). Moreover, the following proportions were also calculated: a) people aged 18 years or over with blood pressure ≥ 140/90 mmHg at the time of the survey, according to any previous medical diagnosis of hypertension (yes or no); b) people aged 18 years or over with blood pressure ≥ 140/90 mmHg who reported having used medications for controlling high blood pressure over the past 15 days (yes or no); and c) people aged 18 years or over with blood pressure ≥ 140/90 mmHg who reported having gone to a doctor because of hypertension over the past year (yes or no).

The survey was approved by the National Ethics Commission for Research Involving Human Beings, of the Ministry of Health, under report number 328,159 of June 26, 2013. The free and informed consent statement was signed in the smartphone itself during the PNS.

RESULTS

The analysis on high blood pressure at the time of measurement within the PNS in 2013, i.e. systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg, indicated that the prevalence of people with high blood pressure was 22.8%.

It was found that 20.0% (95% CI: 19.3-20.8) of the women had high blood pressure, while the prevalence among men was 25.8% (95% CI: 24.8-26.7). The frequency of high blood pressure increased with age, for both sexes, reaching around 47% among people aged 75 years or over. Between the ages of 18 and 74 years, men presented higher blood pressure than women, but the prevalences became equal after the age of 75 years (**Table 1**).

The frequencies were higher in the southeastern and southern regions of Brazil for both men and women (**Table 1**). In all the federal states, the frequency of people with blood pressure ≥ 140/90 mmHg was greater among men. The prevalence among the adult population ranged from 13.3% in Amazonas to 27.6% in Rio Grande do Sul (**Table 2**).

Among the individuals who presented high blood pressure (≥ 140/90 mmHg), 43.2% (95% CI: 41.6-44.8) reported having a previous diagnosis of hypertension, while 56.8% did not know

Table 1. Prevalence of individuals with high blood pressure in the adult population according to age group, region and sex, in the National Health Survey (Pesquisa Nacional de Saúde, PNS), 2013

	Prevalence of individuals aged 18 years or over with high blood pressure at the time of the survey (%)								
	Total			Sex					
				Male			Female		
	Prevalence	95% confidence interval		Prevalence	95% confidence interval		Prevalence	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Age groups									
Total	**22.8**	**22.1**	**23.4**	**25.8**	**24.8**	**26.7**	**20.0**	**19.3**	**20.8**
18 to 24 years	5.9	5.0	7.1	9.1	7.3	11.2	2.7	2.1	3.7
25 to 29 years	10.1	8.8	11.6	14.3	12.0	16.8	5.7	4.6	7.0
30 to 34 years	13.8	12.4	15.4	17.1	14.6	19.8	10.7	9.2	12.5
35 to 44 years	19.1	17.9	20.4	24.0	22.0	26.0	14.9	13.5	16.4
45 to 54 years	29.2	27.6	30.8	33.6	31.3	36.1	25.2	23.3	27.2
55 to 64 years	35.9	34.0	37.8	39.1	36.3	41.9	33.1	30.7	35.6
65 to 74 years	43.1	40.7	45.5	44.8	41.0	48.6	41.8	38.6	45.0
75 years and over	47.1	44.1	50.2	46.2	41.3	51.3	47.8	43.9	51.7
Region									
Total	**22.8**	**22.1**	**23.4**	**25.8**	**24.8**	**26.7**	**20.0**	**19.3**	**20.8**
North	14.6	13.4	15.8	16.4	14.7	18.2	12.7	11.3	14.3
Northeast	21.0	20.1	21.9	24.2	22.7	25.8	18.1	17.0	19.2
Southeast	25.0	23.8	26.1	28.4	26.6	30.2	21.9	20.6	23.3
South	25.0	23.5	26.5	27.3	25.1	29.5	22.8	21.0	24.7
Center-West	20.0	18.8	21.2	22.8	21.0	24.6	17.3	15.8	19.0

that they had high blood pressure. Among those with a previous medical diagnosis of hypertension, 81.4% (95% CI: 79.5-83.2) were using medication, and 69.6% (95% CI: 67.3-71.8) had visited a doctor during the past year (**Figure 1**).

These percentages differed according to sex. Women presented greater occurrence of previous medical diagnoses of hypertension (52.6%; 95% CI: 50.6-54.7) than men (35.2%; 95% CI: 33.1-37.3). Women also used more medication for hypertension (86.8%; 95% CI: 84.8-88.7) than men (74.5%; 95% CI: 71.2-77.6) and visited a doctor more often (74.1%; 95% CI: 71.4-76.7) than men (63.8%; 95% CI: 60.3-67.1) (**Figures 2** and **3**).

DISCUSSION

This was the first national study indicating results from blood pressure measurements among the Brazilian population. One fourth of the male adult population presented blood pressure ≥ 140/90 mmHg, while high blood pressure affected one fifth of the female adult population. Its frequency increased with age, reaching almost half of the elderly population (over 75 years). Blood pressure levels were higher in the southeastern and southern regions of the country, among both men and women. In all the federal states, blood pressure ≥ 140/90 mmHg occurred more

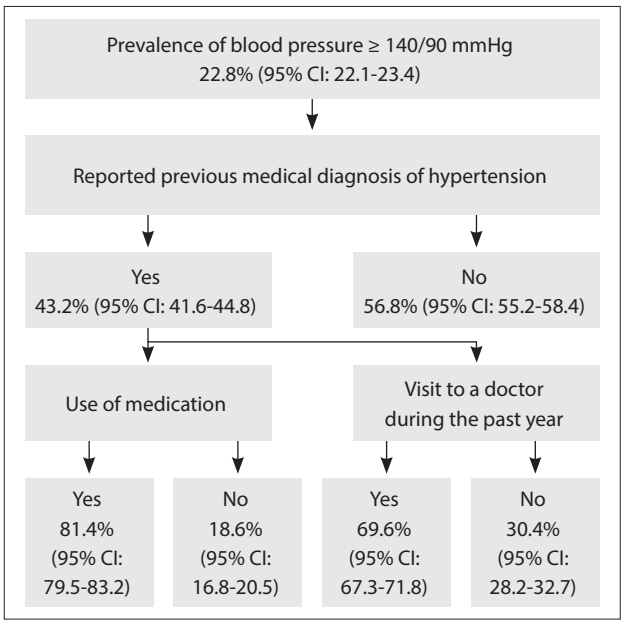

Figure 1. Flow diagram for the whole population with blood pressure ≥ 140/90 mmHg, according to previous medical diagnosis, use of medication and consultations with a doctor during the past year, in the National Health Survey (Pesquisa Nacional de Saúde, PNS), 2013.

Table 2. Prevalence of individuals with high blood pressure among the total number of individuals aged 18 years or over in each federal state, according to sex, in the National Health Survey (Pesquisa Nacional de Saúde, PNS), 2013

Federal states	Total high blood pressure			Male			Female		
	%	Lower limit	Upper limit	%	Lower limit	Upper limit	%	Lower limit	Upper limit
Total	**22.8**	**22.1**	**23.4**	**25.8**	**24.8**	**26.7**	**20.0**	**19.3**	**20.8**
Rondônia	15.6	14.0	17.4	17.2	14.3	20.5	14.0	12.1	16.2
Acre	15.6	13.9	17.6	18.7	15.8	21.9	12.8	10.8	15.1
Amazonas	13.3	11.7	15.1	16.4	13.9	19.1	10.2	8.3	12.6
Roraima	15.3	13.5	17.3	19.5	16.8	22.6	11.0	8.9	13.5
Pará	14.5	12.5	16.9	15.7	12.7	19.3	13.4	10.8	16.5
Amapá	16.4	14.1	19.0	17.6	14.7	20.9	15.3	12.4	18.9
Tocantins	14.7	12.7	16.9	16.8	13.6	20.5	12.6	9.9	16.0
Maranhão	17.2	14.3	20.5	19.9	15.9	24.6	14.6	11.3	18.8
Piauí	18.3	15.9	20.9	20.2	16.9	24.0	16.4	13.5	19.8
Ceará	20.5	18.6	22.5	23.9	21.0	27.0	17.3	15.1	19.8
Rio Grande do Norte	19.1	16.8	21.7	22.1	18.6	26.1	16.5	13.6	19.9
Paraíba	21.3	19.0	23.9	23.3	19.8	27.3	19.5	16.3	23.1
Pernambuco	21.1	19.2	23.2	23.9	21.2	26.8	18.7	16.4	21.1
Alagoas	20.5	18.4	22.6	22.8	19.5	26.3	18.4	15.7	21.5
Sergipe	22.7	20.5	25.1	25.7	22.5	29.2	19.9	17.3	22.9
Bahia	23.5	21.1	26.1	28.0	23.7	32.6	19.6	17.1	22.4
Minas Gerais	24.8	22.1	27.8	29.1	24.8	33.7	21.0	18.0	24.3
Espírito Santo	22.0	19.4	25.0	23.4	19.0	28.6	20.8	18.1	23.8
Rio de Janeiro	27.5	25.6	29.4	30.7	27.8	33.8	24.8	22.8	27.0
São Paulo	24.3	22.7	25.9	27.6	25.2	30.2	21.3	19.3	23.4
Paraná	21.8	19.4	24.3	23.2	20.2	26.5	20.4	17.7	23.5
Santa Catarina	25.6	22.3	29.2	26.1	21.5	31.3	25.1	20.7	30.1
Rio Grande do Sul	27.6	25.3	30.0	31.8	28.3	35.5	23.8	21.2	26.5
Mato Grosso do Sul	26.3	24.0	28.7	29.9	26.2	33.9	22.9	20.3	25.7
Mato Grosso	18.2	15.5	21.2	21.3	17.3	25.9	15.1	12.0	18.9
Goiás	19.5	17.6	21.6	21.9	19.2	25.0	17.2	14.5	20.2
Distrito Federal	17.6	15.6	19.7	20.2	17.0	23.7	15.4	12.9	18.1

frequently among men. The lowest prevalence was found in the state of Amazonas, while the highest was observed in the state of Rio Grande do Sul. Nearly half of the population reported having previous medical diagnoses of hypertension and, out of this portion, over three quarters reported using medication for high blood pressure and close to two thirds had visited a doctor during the past year for their high blood pressure to be monitored, thus demonstrating that they were receiving regular medical follow-up. Women used more medication than men and went to a doctor more often for their high blood pressure to be monitored.

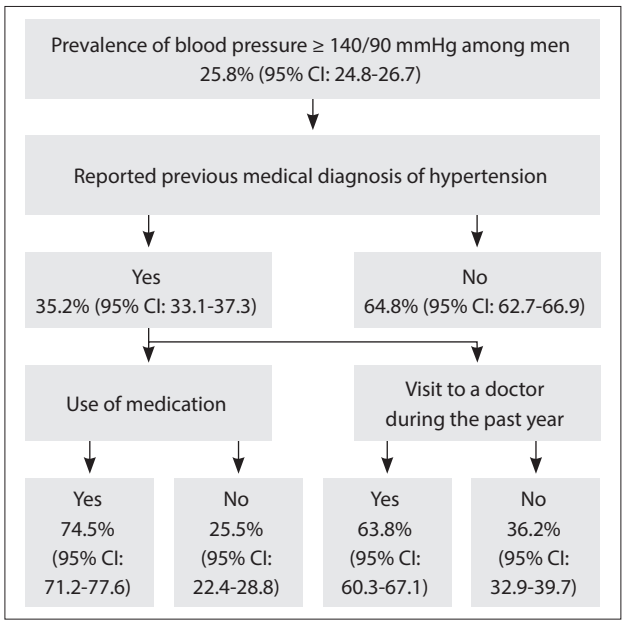

Figure 2. Flow diagram for the male population with blood pressure ≥ 140/90 mmHg, according to previous medical diagnosis, use of medication and consultations with a doctor during the past year, in the National Health Survey (Pesquisa Nacional de Saúde, PNS), 2013.

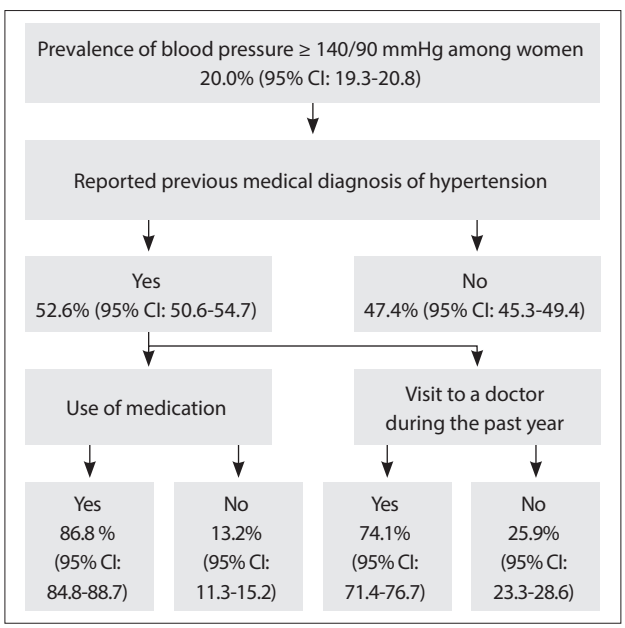

Figure 3. Flow diagram for the female population with blood pressure ≥ 140/90 mmHg, according to previous medical diagnosis, use of medication and consultations with a doctor during the past year, in the National Health Survey (Pesquisa Nacional de Saúde, PNS), 2013.

The PNS provided nationwide blood pressure measurement in Brazil for the first time, using methodology indicated in the literature. Use of digital electronic devices is widely recommended for population-based surveys, given that they reduce measurement errors and make it easier to interpret and standardize the results.[14,15]

A review study involving 35 developing countries identified 204 articles and, similarly to PNS, found greater mean prevalence of hypertension among men, reaching 32.2%, than among women, 30.5%.[16] Greater frequency of high blood pressure among men is concordant with the data from the World Health Organization (WHO) for the year 2008, which demonstrated that among adults over the age of 25 years, the overall prevalence is higher among men (29.2%) than among women (24.8%).[1] The same was found solely in the Americas, with 26.3% for men and 19.7% for women.[1]

There are divergences in the results regarding differences between the sexes, which may occur due to factors such as educational level, race/skin color, obesity, seeking of health services and adherence to treatment, among others.[17] A cross-sectional study on a population-based sample of 1,439 adults ≥ 20 years of age, in Salvador, Brazil, found the opposite: greater prevalence of hypertension among women (31.7%; 95% CI: 28.5-34.9) than among men (27.4%; 95% CI: 23.9-31.2). It also reported that the factors associated with hypertension among women were mixed or black skin color, abdominal obesity, diabetes and the menopause.[17] In the literature, higher blood pressure among women after the menopause is partly attributed to the protective hormonal effect that estrogen confers on women during their fertile phase, which stops after the menopause. Another explanatory factor for increasing hypertension with increasing age might be central obesity.[17]

The PNS also confirmed what had already been described in the literature, regarding increased prevalence of high blood pressure with age. This higher prevalence is due to the changes inherent to growing older, with greater stiffening of the arteries, greater peripheral vascular resistance and comorbidities among the elderly.[17-20]

The present study showed regional differences according to federal state and region, with greater prevalence in the southeast and south. In addition to demographic factors such as the greater participation of elderly individuals in these regions, other risk factors need to be better studied.[21]

The highest frequency among the federal states was in Rio Grande do Sul, followed by Rio de Janeiro, which can be explained

because they are states with large proportions of elderly people;[22] while the lowest was in Amazonas. A previous study carried out within the Pró-Saúde movement at a university in Rio de Janeiro, in 2001, found that the prevalence for both sexes was 29.6% and that it increased significantly with age.[23] On the other hand, the lower prevalence observed in Amazonas can be explained by the lower proportion of elderly individuals in this state and the greater proportion of young people, as indicated in the demographic census.[22]

Studies have indicated that detection, treatment and control of high blood pressure are fundamental for reducing the incidence of cardiovascular events.[17-19] The present study found that 43.2% of the subjects had previously received a medical diagnosis of high blood pressure. The proportion was higher among women, who also had greater frequencies of use of medication and routine medical consultations. One reason why almost half the population with blood pressure ≥ 140/90 mmHg had not previously received a medical diagnosis could be the fact that hypertensive disease is silent and, thus, might lead to a lower demand for healthcare services.[7] The fact that women are more frequently diagnosed and treated has also been pointed out in studies, through the observation that women tend to seek medical services more frequently and therefore have more opportunities for diagnosis, as well as greater adherence to treatment.[3,7,8]

A review study[16] showed that among people with high blood pressure, the proportion of people who were undergoing treatment was low, reaching 29.2% for men and 40.5% for women, while medical follow-up for hypertension among men was 9.8% and among women 16.2%. These findings are in agreement with the present study.

Other PNS analyses have already indicated that only 3% of individuals in the adult population have never had their blood pressure measured and that, therefore, other opportunities for diagnosing high pressure had previously existed.[14] The PNS has also revealed that in Brazil, in general, 95.4% of the population that sought medical assistance over the preceding 15 days had managed to be seen, and that the National Health System has greatly contributed towards this access to healthcare services. Family healthcare services and health insurance also provide wide coverage for the population. However, the quality of these services needs to be improved, through application of simple measures such as blood pressure measurement at all medical consultations and healthcare services, both public and private.

Other indicators such as definitions for hypertensive patients based on correlating high blood pressure and use of medications have been described in the literature.[10,11,19] In the present study, measured blood pressure ≥ 140/90 mmHg was used because this is the indicator used by WHO to monitor countries, with a view to attainment of the goal of reducing hypertension by 25% between 2015 and 2025.[23]

Among the limitations of the present investigation, this was an epidemiological study using a standardized technique to make three sequential measurements using a digital device. The measurements were made by trained interviewers and not doctors, and the stethoscope method of blood pressure measurement was not used.[24] Therefore, there may have been differences due to the different methods for casual blood pressure measurement. There have been reports in the literature of peaks in blood pressure at the time of measurement, also known as white coat syndrome, due to anxiety towards blood pressure measurements, thereby possibly resulting in momentary peaks.[25] Such occurrences were probably minimal, since the measurements were made by researchers and not doctors. Regarding previous diagnoses and use of medication, since this information was self-reported by the interviewees, there may have been differences in their comprehension or memory bias, among other factors.

CONCLUSION

In 2013, the Global Action Plan for the Prevention and Control of Non-communicable Diseases was approved by the World Health Assembly. The plan included a set of indicators for combating these diseases, and reduction of high blood pressure was among these. The PNS constitutes the baseline for this indicator, which takes into consideration the frequency of the population with blood pressure ≥ 140/90 mmHg.[23] These results are very important in relation to monitoring overall targets for reducing hypertension. To reach a relative reduction of 25% in the prevalence of high blood pressure, interventions are needed in order to reduce the consumption of salt and saturated fat, as well as to increase the consumption of fruits and vegetables, along with efforts to decrease the incidence of overweight and obesity and to implement monitoring for early detection and treatment for hypertensive individuals.[23,26]

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Sources of funding: Ministry of Health
Conflict of interests: None

Date of first submission: October 14, 2015
Last received: November 5, 2015
Accepted: November 9, 2015

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Hirschsprung disease and hepatoblastoma: case report of a rare association

Doença de Hirschsprung e hepatoblastoma: relato de caso de uma associação rara

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KEY WORDS:
Hirschsprung disease.
Hepatoblastoma.
Intestinal atresia.
Hearing loss, sensorineural.
Cataract.

PALAVRAS-CHAVE:
Doença de Hirschsprung.
Hepatoblastoma.
Atresia intestinal.
Perda auditiva neurossensorial.
Catarata.

ABSTRACT

CONTEXT: Hirschsprung disease is a developmental disorder of the enteric nervous system that is characterized by absence of ganglion cells in the distal intestine, and it occurs in approximately 1 in every 500,000 live births. Hepatoblastoma is a malignant liver neoplasm that usually occurs in children aged 6 months to 3 years, with a prevalence of 0.54 cases per 100,000.

CASE REPORT: A boy diagnosed with intestinal atresia in the first week of life progressed to a diagnosis of comorbid Hirschsprung disease. Congenital cataracts and sensorineural deafness were diagnosed. A liver mass developed and was subsequently confirmed to be a hepatoblastoma, which was treated by means of surgical resection of 70% of the liver volume and neoadjuvant chemotherapy (ifosfamide, cisplatin and doxorubicin).

CONCLUSION: It is known that Hirschsprung disease may be associated with syndromes predisposing towards cancer, and that hepatoblastoma may also be associated with certain congenital syndromes. However, co-occurrence of hepatoblastoma and Hirschsprung disease has not been previously described. We have reported a case of a male patient born with ileal atresia, Hirschsprung disease and bilateral congenital cataract who was later diagnosed with hepatoblastoma.

RESUMO

CONTEXTO: A doença de Hirschsprung é uma desordem do desenvolvimento do sistema nervoso entérico, que é caracterizada pela ausência de células ganglionares no intestino distal, ocorrendo em cerca de 1 a cada 500.000 nascimentos. O hepatoblastoma é uma neoplasia maligna do fígado que geralmente ocorre em crianças de 6 meses a 3 anos, com prevalência de 0,54 casos por 100.000.

RELATO DE CASO: Um menino com diagnóstico de atresia intestinal na primeira semana de vida evoluiu com diagnóstico concomitante de doença de Hirschsprung. Catarata congênita e surdez neurossensorial foram diagnosticadas. Surgiu lesão hepática com posterior confirmação de hepatoblastoma, tratado com ressecção cirúrgica de 70% do volume hepático e quimioterapia neoadjuvante (ifosfamida, cisplatina e doxorubicina).

CONCLUSÃO: Sabe-se que a doença de Hirschsprung pode estar associada a síndromes de predisposição ao câncer, da mesma forma que o hepatoblastoma já foi correlacionado a certas síndromes congênitas malformativas. No entanto, até o momento, a associação de hepatoblastoma com a doença de Hirschsprung não foi descrita. Relatamos o caso de um menino que nasceu com atresia ileal, doença de Hirschsprung, catarata congênita bilateral e com posterior diagnóstico de hepatoblastoma.

INTRODUCTION

Hirschsprung disease is an unusual, but well-recognized cause of chronic constipation in children. It occurs in approximately 1 in every 500,000 live births, and most commonly presents as a neonatal bowel obstruction. However, in older children, it may present as chronic constipation or enterocolitis.[1] Hirschsprung disease occurs as an isolated trait in 70% of the patients, is associated with a chromosomal abnormality in 12% and occurs with additional congenital anomalies in 18%.[2]

Primary hepatic malignancies account for approximately 1% of cancers in children, and can be divided into two major histological subgroups: hepatoblastoma and hepatocellular carcinoma.[3] The overall prevalence of hepatoblastoma is 0.54 per 100,000 individuals, and it occurs primarily in children younger than 5 years of age.[4] In Brazil, the median age-adjusted incidence rate (AAIR) of hepatoblastoma ranged from 0.0 to 2.8 per million in a study that included data from 13 cities; notably, the highest incidence was found in our city (Porto Alegre), with a median AAIR of 2.78.[5] We report a case of hepatoblastoma in a child previously diagnosed with ileal atresia and Hirschsprung disease, which is an unusual association.

CASE REPORT

A male infant was born after 28 weeks of gestation with a birth weight of 910 grams and Apgar scores of 4 at the first minute and 7 at the fifth minute. At 2 days of age, still without bowel movements, he developed abdominal distension and vomiting. Abdominal radiography showed severe small-bowel distension and wall edema without pneumoperitoneum. Oral feeding was discontinued and antibiotics and total parenteral nutrition were started due to clinical suspicion of necrotizing enterocolitis. A barium enema revealed a state of microcolon due to disuse. On laparotomy, intestinal atresia in the terminal ileum and a disconnected cecum were identified. Ileostomy and cecostomy were performed, and a set of biopsies was obtained, going from the transverse colon to the rectum. Histopathological examination revealed absence of ganglion cells in the rectum and sigmoid colon, consistent with Hirschsprung disease (**Figure 1**). A Duhamel procedure was performed, with total colectomy due to absence of ganglion cells throughout the colon, which was identified during frozen section examination.

During a routine physical examination, the patient was diagnosed with congenital cataracts, which were surgically corrected. Genetic evaluation was normal and TORCH (*Toxoplasma gondii*, rubella, cytomegalovirus, herpes simples and other viruses) complex screening was negative. An echocardiogram showed a large patent ductus arteriosus with hemodynamic impairment. Indomethacin treatment was unsuccessful, and surgical closure was performed. Furthermore, the patient was evaluated by a speech therapist and deafness was detected.

At the age of 25 months, during computed tomography (CT) on the chest to evaluate a lung malformation, a tumor in the right hepatic lobe measuring 5.6 cm x 4.3 cm, with marked contrast uptake, was incidentally observed (**Figure 2**). A liver biopsy was performed, and subsequent immunohistochemical examination of the biopsy specimen revealed epithelial-type hepatoblastoma (**Figures 3, 4** and **5**). The patient was started on neoadjuvant chemotherapy with ifosfamide, cisplatin and doxorubicin (four cycles). At that time, the alpha-fetoprotein (AFP) level was 8229 ng/ml (reference range: < 10 ng/ml). An abdominal CT

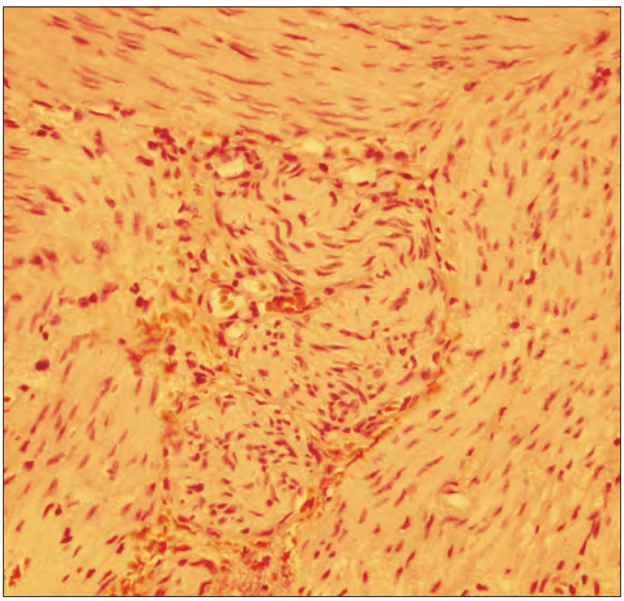

Figure 1. Hirschsprung disease: myenteric plexus lacking ganglion cells (hematoxylin-eosin staining, 400 x).

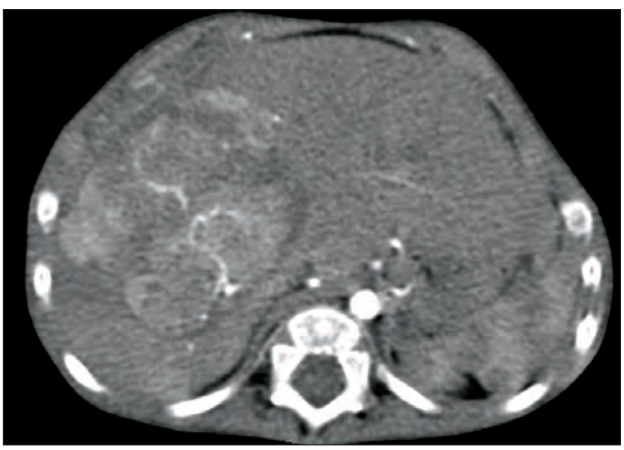

Figure 2. Computed tomography (CT) scan of the abdomen. A space-occupying lesion is visible in the liver, located between the middle and right hepatic veins (segment VIII).

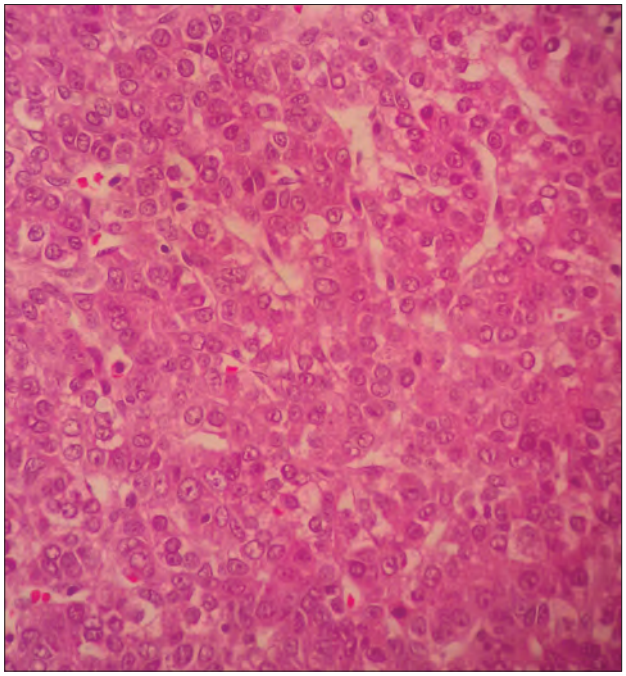

Figure 3. Hepatoblastoma, epithelial type (hematoxylin-eosin staining, 400 x).

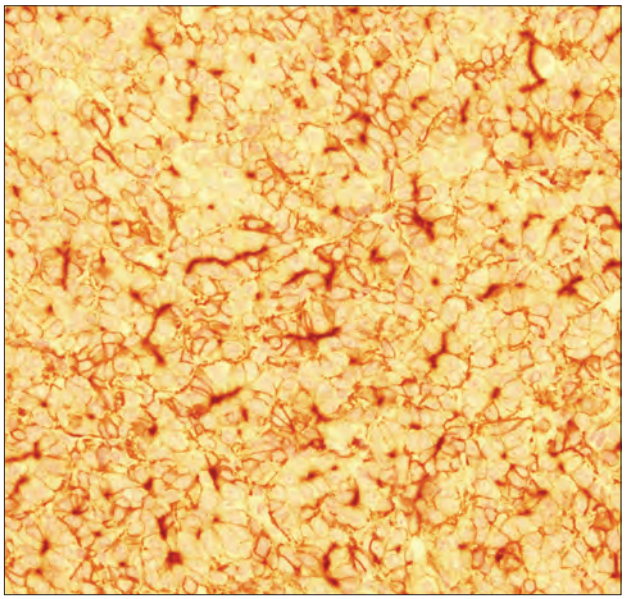

Figure 4. Hepatoblastoma immunohistochemistry: positive for carcinoembryonic antigen (CEA), with canalicular pattern, 400 x.

scan performed after chemotherapy showed a significant reduction in tumor volume (3.2 cm x 2.6 cm). Right hepatectomy was performed, leaving a residual liver of 30%, followed by two cycles of adjuvant chemotherapy. Currently, the patient is asymptomatic, with no evidence of tumor recurrence, he has normal bowel movements and normal AFP level (2.79 ng/ml).

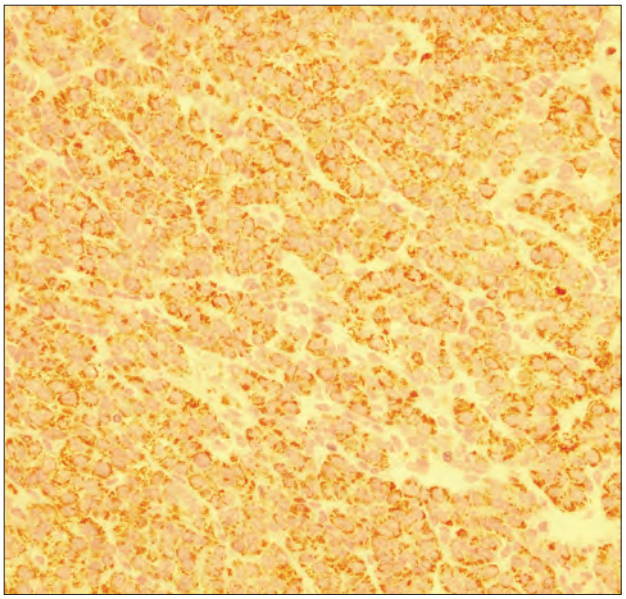

Figure 5. Hepatoblastoma immunohistochemistry: cytoplasmic positivity for Hep Par1, with granular pattern, 400 x.

DISCUSSION

Hirschsprung disease is a developmental disorder of the enteric nervous system that is characterized by absence of ganglion cells in the myenteric (Auerbach's) and submucosal (Meissner's) plexuses of the distal intestine, which results in lack of peristalsis and functional intestinal obstruction.[6] In 80-85% of the cases, the aganglionic region is limited to the rectum and sigmoid colon, as in our patient.[7]

The heterogeneous nature of Hirschsprung disease seems to be supported by evidence of mutations in a variety of genes. The most commonly identified gene is the *RET* proto-oncogene, which is commonly found in familial and long-segment disease. It remains unclear how these mutations result in aganglionosis, but there is some evidence that early neuronal cell death may be a prominent mechanism. Hirschsprung disease is associated with a variety of other congenital abnormalities: malrotation, genitourinary abnormalities, congenital heart disease, limb abnormalities, mental retardation and dysmorphic features.[6] Many of these patients also have other abnormalities of neural crest-derived tissues, such as pigmentation disorders and sensorineural deafness, including Waardenburg syndrome.[6] However, the association of Hirschsprung disease with profound congenital deafness in the absence of other syndromic features, as in our patient, has been reported before.[8,9] In the present case, our patient presented with sensorineural deafness and bilateral congenital cataracts, but no pigmentation disorders.

Hirschsprung disease may also be associated with syndromes predisposing towards cancer, such as familial medullary thyroid carcinoma, multiple endocrine neoplasia type 2A and type 2B and neuroblastoma. A review of the literature was conducted through

an online search for the MeSH, EMTREE and MeSH/DeCS terms "Hirschsprung disease" and "hepatoblastoma" in PubMed, Embase (via Elsevier) and LILACS (via Bireme), respectively (**Table 1**), but did not find any previous reports of comorbid Hirschsprung disease and hepatoblastoma. On the other hand, hepatoblastoma may also be associated with certain congenital syndromes (such as Beckwith-Wiedemann syndrome and trisomy 18 syndrome).[10,11]

The incidence of hepatoblastoma in the United States (2.2 cases per 1 million children aged 0-14 years, over the period 2006-2010[12]) appears to have doubled over recent decades.[13] The cause of this increase in incidence is unknown, but it may be related to increasing survival of very low birth weight premature infants.[14] In Brazil, there have been very few cases, and they are recorded in only 8 of the 14 population-based cancer registries. The incidence appears to be highest in the central-western region of the country.[14,15] The patient in this case report met the criteria for the highest risk of hepatoblastoma (male, white and extremely premature, with birth weight < 1 kg).[16,17]

One sensitive but nonspecific biomarker for the presence of hepatoblastoma is AFP. This is a useful clinical marker for monitoring treatment effectiveness and tumor recurrence, since 90% of the patients at diagnosis have highly elevated serum levels of AFP.[11] Because the liver has excellent regeneration capacity, up to 80% of this organ can be resected.[3] The goal of therapy for hepatoblastoma is complete surgical resection[3] (which was the result achieved in the case reported here), because the majority of patients survive if a hepatoblastoma is removed completely. The overall 5-year survival rate for children with hepatoblastoma is 70%.[12] Metastases are found in approximately 20% of patients at diagnosis (usually in the lungs, central nervous system (CNS) and eyes).[15]

CONCLUSION

We have reported a case of an unusual association of hepatoblastoma in a child with previous diagnoses of Hirschsprung disease, ileal atresia, deafness and cataracts. Complete resection of the tumor was achieved, with favorable clinical evolution. We emphasize the importance of comprehensive assessment of patients with Hirschsprung disease, due to the possibility of several chromosomal abnormalities and associated congenital anomalies.

Table 1. Database search results for Hirschsprung disease and hepatoblastoma on August 6, 2014

Electronic databases	Search strategies	Results
Medline (PubMed)	(Hirschsprung Disease) AND (Hepatoblastoma)	No original articles, case reports or review articles
Embase (Elsevier)	(Hirschsprung Disease) AND (Hepatoblastoma)	No original articles, case reports or review articles
Lilacs (Bireme)	(tw:(Hirschsprung Disease OR Enfermedad de Hirschsprung OR doença de Hirschsprung)) AND (tw:(Intestinal Atresia OR atresia intestinal OR atresia intestinal)) AND (tw:(Hepatoblastoma OR Hepatoblastoma OR Hepatoblastoma))	No original articles, case reports or review articles

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Sources of funding: None
Conflict of interest: None

Date of first submission: July 7, 2014
Last received: Ocotober 17, 2014
Accepted: November 3, 2014

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DOI: 10.1590/1516-3180.2014.00052608

Malignant catatonia responsive to low doses of lorazepam: case report

Catatonia maligna responsiva a baixas doses de lorazepam: relato de caso

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KEY WORDS:
Catatonia.
Benzodiazepines.
Lorazepam.
Depressive disorder.
Case reports [publication type].

PALAVRAS-CHAVE:
Catatonia.
Benzodiazepinas.
Lorazepam.
Transtorno depressivo.
Relatos de casos.

ABSTRACT

CONTEXT: Catatonia can be divided into non-malignant or malignant. The latter is characterized by autonomic instability, exhibiting high fever, tachycardia and hypertension, and is regarded as a fulminant and rapidly progressive subtype.

CASE REPORT: This article reports a case of malignant catatonia in a 43-year-old patient who had been presenting psychiatric disorders for the last three years. The patient was stable, maintaining mutism, immobility and autonomic abnormalities. Oral lorazepam (1 mg every eight hours) was introduced and, in a few hours, the patient became afebrile. Two days later, the patient was already responding to verbal commands.

CONCLUSIONS: Early intervention with lorazepam reduced the evolution of this patient to a fatal complication. Therefore, this case report sought to show that early diagnosis and intervention reduced the occurrence of serious and irreversible clinical outcomes.

RESUMO

CONTEXTO: A catatonia pode ser dividida em não maligna ou maligna. A maligna se caracteriza pela instabilidade autonômica, exibindo febre elevada, taquicardia e hipertensão, além de ser considerada um subtipo fulminante e rapidamente progressivo.

RELATO DE CASO: Este artigo relata um caso de catatonia maligna em paciente de 43 anos, com transtornos psiquiátricos há três anos. A paciente estava estável, mantendo o mutismo, a imobilidade e as anormalidades autonômicas. Foi introduzido lorazepam, via oral, 1 mg de oito em oito horas, e em algumas horas, a paciente ficou afebril. Em dois dias, já estava respondendo a comandos verbais.

CONCLUSÕES: Intervenção precoce com lorazepam preveniu a evolução desta paciente para um desfecho fatal. Portanto, este relato de caso mostrou que o diagnóstico e a intervenção precoces reduziram a ocorrência de desfechos graves e irreversíveis.

INTRODUCTION

Catatonia is a serious syndrome that is present in approximately 9.8% of hospitalized adult psychiatric patients. This syndrome should be considered as a differential diagnosis among patients with signs of mutism, immobility, rigidity and autonomic abnormalities, such as fever, increased pressure blood pressure, tachycardia, tachypnea, leukocytosis and increased kinase creatine.[1-3]

Studies have shown that use of benzodiazepines is effective in 70% of cases, while electroconvulsive therapy is effective in 85%. There are few case reports on malignant catatonia treated only with lorazepam, although this drug could be the initial treatment of choice, because it is simple and presents considerable response in these patients.[4]

The malignant form of catatonia is considered to be a fatal and rapidly progressive subtype. It is a rare condition that presents subtle signs and symptoms and different etiologies, and is therefore underdiagnosed. This case report seeks to encourage healthcare professionals to suspect this differential diagnosis, which would enable introduction of fast and effective treatment to prevent progression of this condition.[5]

CASE REPORT

A 43-year-old married female patient was brought to our institution by the Emergency Medical Service, from an Integrated Psychiatric Care (Assistência Psiquiátrica Integrada) unit where she had been hospitalized for 13 days with a diagnosis of bipolar disorder, with a current depressive episode with psychotic symptoms and emotionally unstable personality disorder. She was under treatment with lithium carbonate (300 mg, three times a day), valproic acid (250 mg, three times a day), risperidone (2 mg, twice a day), diazepam (10 mg, once a day), omeprazole (20 mg, once a day) and chlorpromazine (according to medical criteria).

She was conscious the night before admission, but was found unconscious and presenting breathing difficulty the next morning. Chest compressions were performed for three minutes, which returned $SatO_2$ (oxygen saturation) from 35% to 90%. No medications were found with the patient.

In the emergency room at Hospital São Paulo, the patient presented Glasgow 3, and she was tachycardic (100 bpm), with hypotension (80 x 50 mmHg), blood glucose of 125 mg/dl and $SatO_2$ of 86%, but without pupil description. Flumazenil was administered, without providing any improvement, and then orotracheal intubation (OTI) was performed.

The electrocardiogram input (ECG) indicated sinus bradycardia and a long QT interval. The computed tomography (CT) scan showed no signs of bleeding or acute ischemia.

At the evaluation, the patient had hypertensive peaks (140 x 70 mmHg), hyperthermia (38.5 °C), increased creatine phosphokinase (CPK) (600 U/l to 1000 U/l), but with the absence of muscle stiffness, twitching or hyperreflexia. Nevertheless, treatment for neuroleptic malignant syndrome was administered, comprising use of bromocriptine (2.5 mg every eight hours) in a nasogastric tube for a few days, without improvement.

The urine sample was sent to the Toxicological Assistance Center, which confirmed the presence of benzodiazepines, with only qualitative results, and suggested the hypothesis of exogenous benzodiazepine intoxication, despite the chronic use of this medication for the patient.

Two days after admission, the patient was transferred to the intensive care unit (ICU), and she presented worsening of her clinical parameters. A new cranial CT scan showed diffuse edema with intracranial hypertension, and therefore treatment without using mannitol was started. After a week, another cranial CT showed no signs of abnormality. Throughout this period, the patient was being monitored by the hospital's neurology service. After the intracranial hypertension had been resolved, a hypothesis of hypoxic encephalopathy was put forward.

The electroencephalogram (EEG) examination showed marked diffuse depression of brain electrical activity. Later, another EEG exam was performed and this showed somatosensory evoked potentials, which made it possible to infer that the patient presented cortical activity and that the EEG would be compatible with a conscious individual, but with a slight downgrade that would be compatible with use of benzodiazepine. The cerebrospinal fluid examination did not show any significant changes.

After 20 days of hospitalization, the patient had two episodes of crying, for approximately 20 minutes, expressing grief, which could not be related to pain, time or presence or absence of family.

A psychiatric assessment was requested in order to evaluate the possibility of interference of psychiatric disorders in the patient's clinical improvement.

According to the family, for the last three years, the patient has been under psychiatric treatment for major depression, bipolar disorder and borderline personality disorder. She had previously attempted suicide with rat poison and had three times tried to slit her wrists over the last three years. She also had had five prior psychiatric hospitalizations, ranging from three to 30 days and averaging 10 days. There were also reports of command auditory hallucinations for suicide. From the history collected from the family, it was only possible to make the hypothesis of severe depressive episodes with psychotic symptoms. There were few criteria for bipolar disorder and cluster B personality disorder. The patient possibly presented a depressive syndrome, but this seemed to be less important than the current clinical situation.

There was still uncertainty regarding suicide attempts, since the patient did not have any medication, there was no reversion

with flumazenil, the urine test was only qualitative, she was a chronic user of benzodiazepine drugs (BDZ) and there were medications on her prescription that could cause a drop in the level of consciousness.

Therefore, the hypotheses were organic mental disorders (hypoactive delirium) and depressive syndrome, and monitoring was maintained. The patient was stable, maintaining mutism, immobility and autonomic abnormalities. The possibility of malignant catatonia was therefore suggested and, considering the risks and benefits, oral lorazepam (1 mg every eight hours) was introduced. The psychiatric diagnosis was based on exclusion, and in this case there was a possibility of clinical improvement with medication.

After the introduction of lorazepam, the patient became afebrile after a few hours and, two days later, was already responding to verbal commands (like shaking hands and moving the upper limbs). Therefore, malignant catatonia remained a hypothesis, possibly associated with hypoxic-ischemic encephalopathy.

DISCUSSION

Kahlbaum described catatonia in 1874 as a single clinical factor composed of motor, emotional and behavioral vegetation.[3] In the top ten prospective studies around the world, catatonic syndrome was identified, on average, in 9.8% of admissions of adult psychiatric patients.[6] The prevalence in psychiatric populations ranges from 6% to 38%, with an average incidence of 15% among the patients hospitalized per year.[7]

There are three forms of catatonia: retarded, excited and malignant.[3] Differentiating the three forms was an important aim of this paper.

Catatonia can also be divided in non-malignant or malignant forms. These differ with regard to the autonomic instability presented by malignant forms, which consists of high fever, tachycardia and hypertension. Speech and thoughts are disorganized, accompanied by intense excitement, cataplexy, mutism, rigidity, stereotypy and posture, and this condition can often be fatal.[3,8] The etiology may be neurological, metabolic or exogenous and may include schizophrenia, mood disorders, general medical conditions, substance suspension and autism, apart from idiopathic causes.[3,9]

Due to the varied clinical picture, the diagnosis of malignant catatonia may be questioned since there are other differential diagnoses that should be discarded, such as neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, akinetic mutism, non-epileptic seizures, incarceration syndrome, Stiff's syndrome, Parkinson's disease, dementia and delirium.[1]

Studies have shown that most catatonic patients present mood disorders, particularly mania. Taylor and Abrams noted that 28% of their patients with bipolar disorder exhibited catatonic features.[1,10] Gelenger correlated catatonia with neurological and general medical conditions, believing that catatonia should be considered to be a syndrome, not a disease.[11]

Benzodiazepines and electroconvulsive therapy (ECT) are considered safe and effective for relieving catatonia.[3] Benzodiazepines can usually relieve catatonic symptoms. Lorazepam is the drug that has been most studied and used in treating catatonia, and it can be administered orally, intramuscularly or intravenously. However, in Brazil, injectable benzodiazepines are not available.[12]

We conducted a systematic search of the literature to look for reports of cases similar to those described. The results are shown in **Table 1**. Some of the cases found are described below. Using the MeSH terms "catatonia" and "lorazepam" to filter the case reports, we found 90 cases in Medline. By excluding the MeSH term "Schizophrenia and Disorders with Psychotic Features" in the same search, we found 69 cases. In another search, we used the term "malignant catatonia", which is not a MeSH term, but by using this to filter the case reports, we found 51 cases in Medline.

Lin and Huang followed up 21 schizophrenic patients who required treatment for catatonia and received a protocol consisting of lorazepam and diazepam. The results showed that 13 patients responded in 2 hours, 18 had already responded after one day and all of them were free of catatonia one week afterwards.[3]

In the general ICU of the Ioannina General Hospital, there were seven patients with the criteria for a diagnosis of catatonic disorder. Lorazepam was administered orally (dose of 2.5-10 mg/day), because the intravenous formulation was unavailable at the hospital. Benzodiazepines are considered to be first-line treatment, and all the patients recovered successfully in 2-18 days.[13]

Ungvari et al. conducted a double-blind study with a control group receiving placebo, among a sample of 18 chronic catatonic schizophrenic patients. Lorazepam was administered at a dose of 6 mg/day for 12 weeks and it was insufficient to reduce the signs or symptoms of catatonia. This shows that the doses required for clinical improvement vary.[14] Some cases of catatonic schizophrenia have been reported to require up to 12.5 mg/day of lorazepam for clinical stabilization.[12,15]

Tibrewal et al. showed that around one third of their patients with catatonia responded completely to a lorazepam dose of 3-6 mg/day for 3-7 days, and an improvement in the symptoms of catatonia was observed in two thirds of the cases analyzed.[4]

ECT is useful in cases that are resistant to pharmacological treatment and present prolonged catatonia.[4,16] Petrides et al. claimed that the results from a combination of lorazepam and ECT are superior to monotherapy.[17]

Rey and Walter found 60 reports describing use of ECT in 396 young patients. Among these, serious complications were rare and the treatment led to improvement in 63% of the depression cases, 80% of the mania cases, 42% of the schizophrenia cases and 80% of the catatonia cases.[18]

Table 1. Systematic search of the literature

Database	Research strategy	Cases/case series	Related cases/case series
Medline (Medical Literature Analysis and Retrieval System Online - via PubMed)	MeSH ("Catatonia") AND ("Lorazepam") Filter: "case reports"	90	21
LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde - via Virtual Health Library)	MeSH ("Catatonia") AND ("Lorazepam) Filter: "case reports"	117	16
Medline (Medical Literature Analysis and Retrieval System Online - via PubMed)	Term ("malignant catatonia") Filter: "case reports"	51	14

Search date: July 22, 2014.

CONCLUSION

Catatonia is not a simple disease to diagnose. It requires not only knowledge among healthcare professionals, but also prompt and effective treatment. In this case report, we acknowledge that the lorazepam doses used were not high. These were administered orally and, unfortunately, there was no ECT available in our hospital. This may have affected the evolution of our patient, since there is evidence that the association of benzodiazepines with ECT has a synergistic effect. Nonetheless, early intervention with lorazepam prevented the evolution of this patient to a fatal complication. Therefore, this case report showed that early diagnosis and intervention reduced the occurrence of serious and irreversible clinical outcomes.

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Sources of funding: None
Conflict of interest: None

Date of first submission: August 12, 2014
Last received: September 30, 2014
Accepted: November 5, 2014

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DOI: 10.1590/1516-3180.2015.02191711

The 5As of healthy pregnancy weight gain: possible applications in the Brazilian context to improve maternal-fetal health

Os 5As do ganho de peso saudável durante a gestação: possíveis aplicações no contexto brasileiro para melhoria da saúde materno-fetal

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It is well-established that women who enter pregnancy at a healthy body weight (i.e. body mass index [BMI] 18.5-24.9 kg/m^2), and whose gestational weight gain (GWG) aligns with evidence-based guidelines, are likely to have fewer antenatal, intrapartum and postpartum complications or challenges. This will positively influence their own health as well as that of their child over the short and long-term.[1] Excess GWG is of particular concern given that it is associated with gestational diabetes mellitus, post-partum weight retention, fetal overgrowth and, downstream, childhood obesity.[2] The prevalence of excess GWG in Brazil has been reported to be up to 52%.[3] Thus, there is a need to promote healthy pregnancy weight gain in an effort to optimize maternal-fetal outcomes and secure the future of public health in Brazil.

A large body of evidence supports the importance of a healthy lifestyle (i.e. healthy eating behaviour, adequate sleep, stress management, regular physical activity and limiting sedentary behaviour) during pregnancy for both mother and fetus.[4] Despite this, there are discrepancies regarding care provider messaging and patient uptake of behavioural recommendations. Primary care providers need simple, easy-to-use frameworks that will help guide the clinical encounter in an attempt to improve dialogue with the end goal of guideline-concordant GWG. The objective of this letter is to describe a tool recently developed by the Canadian Obesity Network in an attempt to harmonize GWG approaches and support women with uptake of healthful behaviour.[5]

This practitioner guide was developed based on evidence, and is called the "5As of Healthy Pregnancy Weight Gain" (http://www.obesitynetwork.ca/pregnancy). It is a modified framework to aid primary care practitioners in helping their patients manage their GWG. The guide is rooted in motivational interviewing techniques, behaviour-change theory, and principles of patient-centeredness. Importantly, it respects the brevity of the clinical encounter during prenatal care. Briefly, the 5As are: **Ask** (for permission to discuss weight); **Assess** (the proximal and distal contextual causes of excess GWG); **Advise** (on risks and management options); **Agree** (on a feasible plan to achieve goals); and **Assist** (women in identifying barriers/facilitators; educate, refer and arrange follow-up).

"Ask" allows the patient to defer the discussion or to stop it from taking place at all. The point is that this is a respectful gesture on the part of the provider, who is in a situation of power. Asking permission to discuss this sensitive topic gives some power back to the patient, who, if in agreement about discussing the topic, will now actually be engaged in the discussion.

"Assess" is when the provider evaluates the guideline concordance of the weight that has been gained. However, it is also about understanding the patient: the proximal and distal contexts that can then lead to meaningful discussions. There is little point in a provider making a recommendation without an understanding of who the patient is and his or her life context.

"Advise" refers to the need to provide advice on a personalized level and in a way that considers the socioeconomic and cultural context of each woman. It is here that this framework

may be a unique addition to the clinician's tool box in Brazil. Ignoring one's bias and making assumptions about a patient's health-related behavior can lead to ineffective interventions and should be thoughtfully considered. For example, asking a woman to change her diet by purchasing healthy food from a vendor located far from her home when she does not have transportation may not be helpful. Here, the recommended "intervention" failed the patient, and not the other way around, so not passing judgement is key to strengthening the patient-provider relationship.

"Agree" alludes to the notion that both the expectant mother and her care team agree on a tentative (behavioral modification) plan that ultimately leads to healthy amounts of weight gain per trimester (this is based on the mother's pre-pregnancy BMI category).

"Assist" is associated with offering education and credible resources that may help each patient to increase self-management, and this capitalizes on allied care providers when available. It is universally accepted that weight management programs are more successful when using an interdisciplinary approach. Care can be appropriately triaged, with the necessary referrals made, such that these choices are made as a team and are appropriate for each woman. Only then can unique social determinants be addressed, with minimization of complications and removal of barriers to healthier pregnancy. Much of this success also depends on arranging follow-up appointments or referrals and tracking behaviour over time.[5]

In summary, the 5As framework can be an alternative to current standard practice with the aims of harmonizing the care provider strategy and guiding healthcare professionals in their practices, while adding a personalized and empathetic approach to the patient encounter. It is strongly recommended that future studies assess the efficacy and effectiveness of the 5As framework's ability to facilitate provider-patient dialogue and improve patient experiences. Only then can we hope to directly translate these into healthier maternal-fetal clinical outcomes (e.g., adequate GWG, less gestational diabetes and other cardiometabolic risk factors, decreased mortality, etc.). Lastly, studies focusing on translation, cultural adaption and validation of the tool are also needed. We look forward to academic discussion on this topic in order to improve the quality of the health care system.

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Conflict of interest: None
Sources of funding: None

Date of first submission: October 28, 2015
Last received: November 16, 2015
Accepted: November 17, 2015

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 DOI: 10.1590/1516-3180.20161342T1

Reduced or modified dietary fat for preventing cardiovascular disease

This is the abstract of a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews 2012, issue 5, art. no. CD002137. DOI: 10.1002/14651858.CD002137.pub3. For full text and details about the authors, see reference 1.

Lee Hooper, Carolyn D. Summerbell, Rachel Thompson, Deirdre Sills, Felicia G. Roberts, Helen J. Moore, George Davey Smith

The independent commentary was written by Luciano Ferreira Drager

ABSTRACT

BACKGROUND: Reduction and modification of dietary fats have differing effects on cardiovascular risk factors (such as serum cholesterol), but their effects on important health outcomes are less clear.

OBJECTIVE: To assess the effect of reduction and/or modification of dietary fats on mortality, cardiovascular mortality, cardiovascular morbidity and individual outcomes including myocardial infarction, stroke and cancer diagnoses in randomised clinical trials of at least 6 months duration.

METHODS:

Search methods: For this review update, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase, were searched through to June 2010. References of Included studies and reviews were also checked.

Selection criteria: Trials fulfilled the following criteria: 1) randomized with appropriate control group, 2) intention to reduce or modify fat or cholesterol intake (excluding exclusively omega-3 fat interventions), 3) not multi factorial, 4) adult humans with or without cardiovascular disease, 5) intervention at least six months, 6) mortality or cardiovascular morbidity data available.

Data collection and analysis: Participant numbers experiencing health outcomes in each arm were extracted independently in duplicate and random effects meta-analyses, meta-regression, sub-grouping, sensitivity analyses and funnel plots were performed.

MAIN RESULTS: This updated review suggested that reducing saturated fat by reducing and/or modifying dietary fat reduced the risk of cardiovascular events by 14% (RR 0.86, 95% CI 0.77 to 0.96, 24 comparisons, 65,508 participants of whom 7% had a cardiovascular event, I2 50%). Subgrouping suggested that this reduction in cardiovascular events was seen in studies of fat modification (not reduction — which related directly to the degree of effect on serum total and LDL cholesterol and triglycerides), of at least two years duration and in studies of men (not of women). There were no clear effects of dietary fat changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 71,790 participants) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, 65,978 participants). This did not alter with sub-grouping or sensitivity analysis. Few studies compared reduced with modified fat diets, so direct comparison was not possible.

AUTHORS' CONCLUSIONS: The findings are suggestive of a small but potentially important reduction in cardiovascular risk on modification of dietary fat, but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear.

The abstract is available free-of-charge from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002137.pub3/abstract.

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COMMENTS

Implications for practice

This systematic review provides important data regarding the impact of diet modification on cardiovascular outcomes (including acute myocardial infarction and stroke). The authors found that dietary changes to reduce saturated fat and partly replace it with unsaturated fats (the ideal type of unsaturated fat is unclear) appears to reduce the incidence of cardiovascular events, but that replacing the saturated fat with carbohydrate (creating a low-fat diet) was not clearly protective (despite modest improvements in weight, body mass index, total and low-density lipoprotein, LDL). The protective effect was seen almost exclusively in men who maintained the dietary modification over a period of at least two years. The reasons why the long-term effect from modifying women's diets was neutral remain unclear. Dietary counseling should be recommended for individuals at high risk of cardiovascular disease (particularly when lipid-lowering medication is unavailable), and probably for low-risk populations as well. Despite the significant impact of reduced or modified dietary fat on cardiovascular events, its effects on total and cardiovascular mortality are much less clear. No evidence was found regarding the long-term effects of altering trans fat intake.

While interventions to alter dietary fat intake in individuals at high cardiovascular risk have been fairly successful, such health promotion initiatives in the general population have been less successful. Further investment is needed to help individuals at high and low cardiovascular risk to make effective changes to dietary fat intake and to maintain these changes over their lifetimes. Continuous efforts to change the current legislation so as to alter the fat content of foods, improve labeling, enable price reductions and provide greater availability of healthier foods, thereby placing food production and processing as priority items for health promotion may yield major advances in this field.

Implications for research

Despite the evidence provided by this systematic review, long-term research to help us understand what types of unsaturated fats are most useful in the diet for replacing saturated fats (monounsaturated fats, polyunsaturated fats and specific fatty acids) is clearly necessary. The financial implications (with cost analyses) and legislation to modify fat intake among individuals at various levels of cardiovascular risk should be assessed and reflected in health policies. It is unclear whether there is any additional benefit in relation to cardiovascular events from modifying dietary fat in individuals at high risk of cardiovascular disease who are on lipid-lowering medication. The relative impact of exercise activity is also not clear in this scenario. There are no studies assessing the long-term health implications of reducing trans fat intake. Most trials have not reported trans fat intake in

intervention groups in randomized studies, such that the evidence relating to the long-term impact of modifying the quantity of trans fat comes from intermediate outcomes only. Thus, long-term clinical trials evaluating the impact of reductions in trans fats would be useful for clarifying these effects on cardiovascular prognoses.

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DOI: 10.1590/1516-3180.20161342T2

Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus

This is the abstract of a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews 2005, issue 2, art. no. CD004095. DOI: 10.1002/14651858.CD004095.pub2. For full text and details about the authors, see reference 1.

Susan L. Norris, Xuanping Zhang, Alison Avenell, Edward Gregg, Tamara Brown, Christopher H. Schmid, Joseph Lau

The independent commentary was written by Adriano Namo Cury

ABSTRACT

BACKGROUND: Most persons with type 2 diabetes are overweight and obesity worsens the metabolic and physiologic abnormalities associated with diabetes.

OBJECTIVE: The objective of this review is to assess the effectiveness of lifestyle and behavioral weight loss and weight control interventions for adults with type 2 diabetes.

METHODS:

Search methods: Studies were obtained from computerized searches of multiple electronic bibliographic databases, supplemented with hand searches of selected journals and consultation with experts in obesity research.

Selection criteria: Studies were included if they were published or unpublished randomized controlled trials in any language, and examined weight loss or weight control strategies using one or more dietary, physical activity, or behavioral interventions, with a follow-up interval of at least 12 months.

Data collection and analysis: Effects were combined using a random effects model.

MAIN RESULTS: The 22 studies of weight loss interventions identified had a 4,659 participants and follow-up of 1 to 5 years. The pooled weight loss for any intervention in comparison to usual care among 585 subjects was 1.7 kg (95 % confidence interval [CI] 0.3 to 3.2), or 3.1% of baseline body weight among 517 subjects. Other main comparisons demonstrated non significant results: among 126 persons receiving a physical activity and behavioral intervention, those who also received a very low calorie diet lost 3.0 kg (95% CI -0.5 to 6.4), or 1.6% of baseline body weight, more than persons receiving a low-calorie diet. Among 53 persons receiving identical dietary and behavioral interventions, those receiving more intense physical activity interventions lost 3.9 kg (95% CI -1.9 to 9.7), or 3.6% of baseline body weight, more than those receiving a less intense or no physical activity intervention. Comparison groups often achieved significant weight loss (up to 10.0 kg), minimizing between-group differences. Changes in glycated hemoglobin generally corresponded to changes in weight and were not significant when between-group differences were examined. No data were identified on quality of life and mortality.

AUTHORS CONCLUSIONS: Weight loss strategies using dietary, physical activity, or behavioral interventions produced small between-group improvements in weight. These results were minimized by weight loss in the comparison group, however, and examination of individual study arms revealed that multicomponent interventions including very low calorie diets or low calorie diets may hold promise for achieving weight loss in adults with type 2 diabetes.

The full text is available free-of-charge from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004095.pub2/abstract

The abstract is also available in the Portuguese and Chinese languages

REFERENCE

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COMMENTS

The systematic review of 22 studies under the title "Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus", by Norris et al.,[1] provides some reflections on how impactful the suggestions for the emphasis on optimization of lifestyle changes are, with regard to improving body weight, quality of life and biochemical markers among patients with type 2 diabetes.

Despite the heterogeneity of the studies involved, there are very few studies in the literature that have eschewed the pharmacological approach in favor of only targeting behavioral changes in habits, with and without physical activity, and thus focusing on weight loss, improvement of glycemic control and the impact on quality of life or even on mortality. Hence, this review will have an impact on this study subject.

The lack of statistical significance does not invalidate the changes in dietary behavior or lifestyle that should guide patients. This review demonstrates that weight loss does take place, but without great magnitude and sustainability beyond 12 months after the intervention. Very low-calorie and stricter diets present some advantages regarding weight loss, but the effect does not persist over long-term follow-up. No statistical strength was found, but there was always a trend towards improvement of weight or glycated hemoglobin levels for patients with type 2 diabetes who underwent intervention and monitoring.

The number of homogeneous studies is certainly insufficient to establish waymarks and rules. Good sense needs to prevail in dietary counseling and physical activity. Even if this non-pharmacological intervention is not shown to have any significant impact on mortality, the set of therapies proposed for patients with type 2 diabetes will certainly have an impact and will give rise to improvement of quality of life and understanding of the disease, even if the weight loss effect becomes diluted with time. There is an ever-present need to seek strategies to control chronic diseases, so as to achieve health benefits that transform the statistics.

It is noteworthy that a recent study in the New England Journal of Medicine[2] showed that the type of diet can indeed make a difference in this type of study. Different paths need to be devised for different patients, so that the full meaning of treatment can be attained.

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Indexing and scope

The São Paulo Medical Journal/Evidence for Health Care was founded in 1932. Its articles are indexed in Medline, Lilacs, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Published bimonthly by the Associação Paulista de Medicina, the journal accepts articles in the fields of clinical health science (internal medicine, gynecology and obstetrics, mental health, surgery, pediatrics and public health). Articles will be accepted in the form of original articles (clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies and systematic reviews with or without meta-analysis), narrative reviews of the literature, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

The Journal's policy and procedures

After receipt of the article by the Scientific Publications Sector, the authors will be provided with a protocol number. This number serves to maintain good understanding between the authors and the Scientific Publications Sector. Following this, the article will be read by the Editor, who will verify whether it is consonant with the journal's policy and interests, i.e. whether the research or review is within the fields of health or public health.

Next, the Scientific Publications Sector will verify whether the text complies with the journal's Instructions for Authors. If the text is incomplete or if it is not organized as required, the authors will be asked to resubmit their text after resolving such problems. When its format is acceptable, the Scientific Publications Sector will submit the manuscript to closed peer review, in which the reviewers will not sign their verdict and will not know the names of the authors. Each paper will be reviewed by at least three reviewers: one expert in the field, one associate editor (who will evaluate the article from the reader's perspective) and one *ad hoc* editorial advisor (who will assess methodological aspects of the study).

The authors will then receive the reviewers' evaluation and will be asked to resolve all the problems that have been pointed out. Once the Scientific Publications Sector receives the manuscript again, the text will be sent to the scientific editor and the proofreader, who will point out problems with sentence construction, spelling, grammar, bibliographical references and other matters. The authors should then provide all further information and corrections requested and should mark in the text all the points at which modifications have been made, using different colors or electronic text marking systems, so that these modifications are easy to see.

When the text is considered acceptable for publication, and only then, it will enter the queue for publication and the author will receive a letter of acceptance of the article. The Scientific Publications Sector will provide a proof, including any tables and figures, for the authors to approve. No article is published without this last procedure.

Instructions for authors

General guidelines: for all types of articles

Texts must be submitted exclusively through the Internet, using the electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript must be submitted in English. Nonetheless, it must also include a summary and five key words both in Portuguese and in English. The key words must be selected from the DeCS and MeSH lists only, as explained in detail below (no other key words will be accepted).

Papers submitted must be original and therefore all the authors need to declare that the text has not been and will not be submitted for publication in any other journal. Papers involving human beings (individually or collectively, directly or indirectly, totally or partially, including the management of information and materials) must be accompanied by a copy of the authorization from the Research Ethics Committee of the institution in which the experiment was performed.

All articles submitted must comply with the editorial standards established in the Vancouver Convention (Uniform Requirements for Manuscripts Submitted to Biomedical Journals)[1] and the specific quality guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE)[5,6] and accuracy studies on diagnostic tests (STARD).[7,8]

The style known as the "Vancouver Style" is to be used not only for the format of the references, but also for the whole text. The Editors recommend that authors should familiarize themselves with this style by accessing http://www.icmje.org.

Abbreviations must not be used, even those in common use. Drugs or medications must be referred to using their generic names, avoiding unnecessary mention of commercial or brand names, and should be followed by the dosage and posology. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses.

Grants, bursaries and any other financial support for studies must be mentioned separately after the references, in a section named "Acknowledgements", along with any other acknowledgements to individuals or professionals who have helped in producing the study but whose contribution does not constitute authorship (we recommend that the item "Authorship" at http://www.icmje.org should be read to obtain clarifications regarding the criteria for authorship).

For any type of study, all statements in the text that are not results from the study presented for publication in the São Paulo Medical Journal/Evidence for Health Care, but are data from other studies already published elsewhere must be accompanied by citations of the pertinent literature. Thus, statements about the incidence or prevalence of diseases, costs, frequency of use of certain therapies

and epidemiological data in general should be followed by the references for the surveys that generated this information, even if the data come from government institutions or databases, given that these are data from other studies.

Format

First page (cover page)

The first page must contain:

1) the type of paper (original article, review or updating article, short communication or letter to the editor);
2) the title of the paper in English and Portuguese, which must be short but informative;
3) the full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations for authors' names must not be used; thus, names should either be sent complete or with middle names omitted, for example: an author whose full name is John Richard Smith can be presented as John Smith or John Richard Smith, but not as John R. Smith; likewise, use Christopher Smith and not Chris Smith, or William Smith and not Bill Smith, and so on)), his/her academic titles (abbreviated in English), in the order obtained (for example: MD for medical doctor, MSc for holders of a master's title, PhD for holders of a doctorate or BSc for bachelor of science, such as in biology), and the positions currently held (for example, Doctoral Student, Attending Physician, Adjunct Professor, Associate Professor, Head of Department, etc.), in the department and institution where he/she works, and the city and country;
4) the place where the work was developed;
5) the complete address (name of street or avenue, building number, city) of the corresponding author, telephone and e-mail that can be published together with the article.
6) the date and place of the event at which the paper was presented, if applicable, such as congresses or dissertation or thesis presentations;
7) sources of support in the forms of finance for the project, study bursaries or funding for purchasing equipment or drugs. The protocol number for the funding must be presented;
8) description of any conflicts of interest held by the authors. We recommend that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest.

Second page: abstract (English and Portuguese) and key words

The second page must include the title and an abstract (English and Portuguese, maximum of 250 words each),[9] structured in five items:

1) context and objective;
2) design (type of study) and setting (place where the study was developed);
3) methods (described in detail);
4) results; and
5) conclusions.

The abstract (both in English and in Portuguese) should contain five key words. The English terms must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which are available on the internet (http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh).[10] The Portuguese terms must be chosen from the *Descritores em Ciências da Saúde* (DeCS), developed by Bireme, which are available on the internet (http://decs.bvs.br/).[11]

References

The list of references (in the "Vancouver style", as indicated by the International Committee of Medical Journal Editors, ICMJE) should be laid out in the final part of the article, after the conclusions and before the tables and figures. In the text, the references must be numbered according to the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences (see examples in the preceding section), and must be in superscript form (without using parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references cited in the text.

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

Article in journal

- Hurt AC, Hardie K, Wilson NJ, et al. Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. N Engl J Med. 2011;365(26):2541-2.

Chapter of book

- Miller WI, Achernabb JC, Fluck CE. The adrenal cortex and its disorder. In: Sperling M. Pediatric endocrinology. 3rd ed. Elsevier Health Sciences; 2008. p. 444-511.

Text on the internet

- Centers for Disease Control and Prevention. Children's food environment State Indicator Report, 2011. Available from: http://www.cdc.gov/obesity/downloads/ChildrensFoodEnvironment.pdf. Accessed in 2012 (Mar 7).

Figures and tables

Images must have good resolution (minimum of 300 DPI) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint documents. If photographs are inserted in a

Microsoft Word file, the images should also be sent separately. Graphs must be prepared in Microsoft Excel (do not send them in image formats) and must be accompanied by the tables of data from which they have been generated. The number of illustrations must not exceed the total number of pages minus one.

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 legend or title sentence should be short but comprehensible without depending on reading the article.

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

São Paulo Medical Journal/Evidence for Health Care is for now published in black-and-white in its printed version. Photographs, photomicrographs, bar and line graphs and any image to be published must be prepared considering that there will be no color differentiation (any color information will be discarded). Shades of gray and printing patterns (dots, stripes and others) should be used instead, with good contrast.

Original articles

Clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies, and systematic reviews with or without meta-analysis, are considered to be original articles.

The São Paulo Medical Journal/Evidence for Health Care 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, from 2008 onwards, manuscripts on clinical trials have been accepted for publication only if they have received an identification number from one of the clinical trial registers that have been validated in accordance with the criteria established by WHO and ICMJE. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal/Evidence for Health Care. The addresses for these registers are available from the ICMJE website (http://www.icmje.org). The identification number should be declared at the end of the abstract.

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;[7,8]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]

The São Paulo Medical Journal takes the view that these guidelines not only aid in writing and organizing the content of articles in a standardized manner, thereby improving their quality and facilitating reading and assessment, but also these guidelines help to avoid situations in which important information on the methodology of studies remains outside of the manuscript.

As a partner institution of the Cochrane Collaboration and the Brazilian Cochrane Center, the *Associação Paulista de Medicina* considers that production of articles in accordance with these guidelines also aids in future production of systematic reviews of the literature and meta-analyses. Thus, articles submitted for publication that are not in accordance with these norms may be returned to their authors for adjustment before the peer review process begins.

Original articles must be structured so as to contain the following parts: Introduction, Objective, Methods, Results, Discussion and Conclusion. The text must not exceed 5,000 words (excluding tables, figures and references), from the introduction to the end of the conclusion, and must include a structured abstract with a maximum of 250 words.[9] "Structured abstract" means that the abstract must contain the following items: Context and objective, Design and setting, Method, Results and Conclusion.

The structure of the document should follow the format laid out below:

1) *Title and abstract*: the study design and/or the way participants were allocated to interventions, for example "randomized" or "retrospective" study, should be mentioned in the title and in the abstract. The abstract should provide a summary of what was done and what was found.
2) *Introduction:* specify the reasons for carrying out the study, describing the present state of knowledge of the topic. Describe the scientific background and "the state of the art". Do not include here any results or conclusions from the study. Use the last paragraph to specify the principal question of the study, and the principal hypothesis tested, if there is one. Do not include discussions about the literature in the introduction; the introduction section should be short.
3) *Objective:* describe briefly what the main objective or question of the study was. Clearly describe the pre-specified hypotheses.
4) *Methods*

4.1) *Type of study*: describe the design of the study and specify, if appropriate, the type of randomization (the way in which draws were conducted), the blinding (how this was ensured), the diagnostic test standards (gold standard or range of normal values) and the time direction (retrospective or prospective). For example: "randomized clinical trial", "double-blind placebo-controlled clinical trial", "cross-sectional accuracy study", "retrospective cohort study", "cross-sectional prevalence study" or "systematic review of clinical trials".

4.2) *Sample, participants or patients*: describe the eligibility criteria for participants (inclusion and exclusion criteria) and the sources and procedures for selection or recruitment. In case-control studies, describe the rationale for distributing the subjects as cases and controls, and the matching criteria. The numbers of patients at the beginning and end of

the study (after exclusions) must be made clear. A flow diagram showing the initial recruitment, the exclusions and the final sample of patients included should be produced and inserted in the article.

4.3) *Setting:* indicate the place where the study was carried out, including the type of healthcare provided (i.e. whether primary or tertiary; and whether in a private or in a public hospital). Avoid stating the name of the institution where the study was developed (for blinding purposes in the peer review). Only the type of institution should be made clear, for example: "public university hospital" or "private clinic".

4.4) *Procedures (*intervention, diagnostic test or exposure): describe the principal characteristics of any intervention, including the method, the timing and the duration of its administration or of data collection. Describe the differences in interventions administered to each group (if the study is controlled). Detail the procedures in such a way that other researchers will be able to repeat them in other localities.

4.5) *Main measurements, variables and outcome*: state what the primary and secondary outcomes analyzed in the study are. Describe the method of measuring the primary result, in the way in which it was planned before data collection. For each variable of interest, detail the assessment methods. If the hypothesis of the study was formulated during or after data collection (and not before), this needs to be declared. Describe the methods used to enhance the quality of measurements (for example, multiple observers, training, etc.) and to avoid bias. Explain how quantitative variables were handled in the analyses.

4.6) *Sample size and statistical analysis*: describe the sample size calculation method, or the study period in the event that patients were consecutively admitted over a period. Readers need to understand why a given number of patients was used. The planned statistical analysis, the statistical tests used and their significance levels, along with any *post hoc* analyses, should be presented in this section. Describe the methods used to control for confounding factors and variables, and explain how missing data and cases lost from the follow-up were dealt with.

4.7) *Randomization*: describe the method used to implement the random allocation sequence (for example, sealed envelopes containing random sequences of numbers or software for generating random numbers). If appropriate, report that the study used "quasi-randomization".[12] In addition, describe who generated the random sequence, who assigned the participants to each group (in the case of controlled trials) and who recruited the participants.

5) *Results:* describe the main findings. If possible, these should be accompanied by their 95% confidence intervals and the exact level of statistical significance (it is not enough to write "$P < 0.05$": the exact P value should be supplied). For comparative studies, the confidence interval must be stated for the differences between the groups.

5.1) *Participant flow diagram*: describe the flow of participants through each stage of the study (inclusions and exclusions) and the follow-up period, and the number of participants completing the study (or lost from the follow-up). Use a flow diagram to demonstrate the numbers of patients, from the initial recruitment to the end of the study, and the reasons for exclusions. If there was any "intention-to-treat" analysis, describe it.

5.2) *Deviations*: if there was any deviation from the protocol, away from what was initially planned, describe it and the reasons for it.

5.3) *Adverse events*: describe any side effect, adverse event or complication.

6) *Discussion:* provide an interpretation of the results, taking into account the study hypotheses and conclusions. Emphasize the new and important factors encountered in the study, which will form part of the conclusion. Do not repeat data presented in the introduction or results in detail. Mention any limitations of the findings that should be noted and any possible implications for future research. Describe any potential bias. Report any relevant findings from other studies: it is important to review the recent literature to seek new evidence that may have been published, which needs to be discussed. State whether the findings can be generalized to populations (i.e. whether the findings have external validity). It is recommended that the last two paragraphs should contain implications for practice and for further research.

7) *Conclusions:* specify only the conclusions that can be sustained by the results, together with their clinical significance (avoiding excessive generalization). Draw conclusions based on the objectives and hypotheses of the study. The same emphasis should be placed on studies with positive and negative results.

Systematic reviews with or without meta-analyses should comply with the same publication norms established for original articles, and be produced in accordance with PRISMA[4] and the Cochrane Collaboration's systematic review Handbook.[13] The text should not exceed 5,000 words (excluding tables, figures and references)

Short communications, case reports or case series

Short communications and case reports must be limited to 3,000 words (from the introduction to the end of the conclusion). 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 thus: Introduction, Objective, Methods, Results, Discussion and Conclusion, like in original articles.

Individual case reports should contain: 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 key words. The abstracts in short communications should be structured with: Context and objective, Design and setting, Methods, Results and Conclusion, like in original articles. The abstracts in case reports and case series should contain: Context, Case Report (with a description of the case and a pertinent discussion) and Conclusion.

The São Paulo Medical Journal/Evidence for Health Care 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.[14] The results from the systematic search of the main databases — Medline (via PubMed), Embase, Lilacs and Cochrane Library — should be presented in a table with the search strategy for each database and the number of articles obtained.

Narrative reviews

Narrative reviews may be accepted by the São Paulo Medical Journal/Evidence for Health Care and should be structured with: Introduction, Objectives, Methods, Results, Discussion and Conclusions. The abstract must be structured with: Context and objective, Design and setting, Methods, Results and Conclusions, like in original articles. The manuscript must comply with the norms of the Vancouver style[1] and must include a systematic search in the main databases: Medline, Embase, Lilacs and Cochrane Library. The search strategy for each database and the number of articles obtained from each database should be presented 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 must be use for Medline, LILACS and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, search strategy must be performed, at the same time, with English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms. 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).

Letters to the editor

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

Documents cited

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13. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. Available from: http://www.cochrane.org/training/cochrane-handbook/. Accessed in 2012 (Aug 6).
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