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## Translation and validation:

- Warmometer, a tool for assessing warmth in patient-provider relationships, for use in Brazilian Portuguese

## A cross-sectional analytical study:

- Helicobacter pylori infection in family members of patients with gastroduodenal symptoms
- Dietary intake of non-dialysis chronic kidney disease patients: the PROGREDIR study

## Review of systematic reviews:

- What do Cochrane systematic reviews say about new practices on integrative medicine

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# Launching the Latin American Epidemiological Cooperation relating to Noncommunicable Diseases

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Latin America and the Caribbean form one of the world's macroregions and comprise 50 independent countries and a few colonies, with a total of approximately 650 million inhabitants. Although these countries have almost twice the population of the United States, the combined gross national product of Latin American and Caribbean countries is only 55% of that of the United States.<sup>1</sup> The socioeconomic differences between Latin American and Caribbean countries and the United States are reflected in educational, health-related and scientific indexes that show Latin American and Caribbean countries unfavorably. The amount of money spent on medical care and, especially, to support medical and health-related research in the United States is immensely greater than in Latin American and Caribbean countries. In contrast, the principle of universal health care coverage that has been adopted in most Latin American and Caribbean countries faces stiff opposition in the United States.<sup>2</sup>

Despite these differences, the epidemiological profile of all countries in the Americas is much closer than what was seen half a century ago. Infectious and parasitic diseases in Latin America have declined with only a few exceptions, such as arbovirus-borne diseases. Likewise, disorders relating to undernutrition and maternal care have faded away in most Latin American and Caribbean countries. Noncommunicable diseases such as cardiovascular, respiratory, renal, mental and osteoarticular diseases have become the most important cause of death, morbidity and disability on both sides of the border between the United States and Latin American and Caribbean countries.<sup>3</sup> One example of this is the astonishingly temporal trends of obesity prevalence observed between Latin American and Caribbean countries and the United States.<sup>4</sup> The epidemiological profile and priorities in Latin American and Caribbean countries were discussed previously on this page, in an analysis on Argentina, Brazil, Colombia and Mexico, using data from the Global Burden of Diseases study. Briefly, the priorities for noncommunicable diseases have been determined to be: (1) control of alcohol intake; (2) detection, treatment and control of hypertension; (3) prevention of stroke and coronary heart disease secondary care; (4) prevention of obesity and diabetes; and (5) screening for chronic kidney disease.<sup>5</sup>

To face the challenge of noncommunicable diseases, strong scientific support from epidemiological studies has been necessary. Despite the enormous contribution of the United States towards the epidemiology of chronic diseases, such as through the seminal Framingham Heart Study,<sup>6</sup> and the contributions made by other countries, the realities of Latin American and Caribbean countries impose a specific approach. Specific longitudinal studies addressing particular issues relating to ethnicity, diet and socioeconomic determinants are needed. Fortunately, the challenge of understanding the determinants of chronic diseases in Latin American and Caribbean countries has indisputably been addressed by local scientists and public health authorities in Argentina,<sup>7</sup> Brazil,<sup>8</sup> Chile,<sup>7,9</sup> Mexico,<sup>10</sup> Peru<sup>11</sup> and Uruguay.<sup>7</sup>

In April 2018, it was possible to organize an initial summit event in Chile, which was called the "First Meeting on Latin American Population-Based Cohorts for Studies on Chronic Diseases" (I Jornada de Cohortes Poblacionales Latinoamericana para el Estudio de Enfermedades Crónicas, COPLAS). This meeting brought together researchers from 12 studies. **Table 1** describes the five ongoing cohort studies in Latin American and Caribbean countries among adults without any specific disease.<sup>7-11</sup>

This meeting marked a big step forward for Latin American and Caribbean investigators working on the epidemiology of non-communicable diseases, towards permanent cooperation. In the near future, this should include more studies in those nations and in other countries. The consequences of this aggregation will allow Latin American and Caribbean epidemiological scientists to carve out a role as significant players worldwide, in issues relating to noncommunicable diseases.

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**Table 1.** Description of five ongoing Latin American cohorts among adults, addressing cardiovascular diseases (CVDs), cancer, diabetes and chronic pulmonary obstructive disease (COPD)

Acronym (reference)	Name	Country	Main aim	Number of participants	Start date	Website
CESCAS <sup>7</sup>	Center for Excellence in Cardiovascular Health in South America	Argentina, Chile and Uruguay	Prevalence, incidence and distribution of risk factors for CVDs, COPD and cancer	7,524 adults in 4 cities in 3 countries aged 35 to 74 years Random sampling	2010	<a href="https://estudiocesca.iecs.org.ar/">https://estudiocesca.iecs.org.ar/</a>
ELSA-Brasil <sup>8</sup>	Brazilian Longitudinal Study of Adult Health	Brazil	Development and progression of clinical and subclinical chronic diseases, particularly CVDs and diabetes.	15,105 civil servants aged 35-74 years in 6 cities in Brazil	2008	<a href="http://www.elsa.org.br/">http://www.elsa.org.br/</a>
MAUCO/ACCDIS <sup>9</sup>	Maule Cohort/ Advanced Center for Chronic Diseases	Chile	Factors involved in development of or protection against CVDs, cancer, diabetes	10,000 unselected adults aged 38 to 74 years from the agricultural town of Molina	2014	<a href="http://www.accdis.cl">http://www.accdis.cl</a>
ESMaestras <sup>10</sup>	Estudio de Salud de la Maestras (Teachers' Health Study)	Mexico	Lifestyle and health factors involved in development of CVDs, cancer and diabetes in women	115,315 female + 2,160 male teachers	2006	<a href="http://www.esmaestras.org/">http://www.esmaestras.org/</a>
Cronicas <sup>11</sup>	Centro de Excelencia en Enfermedades Cronicas, Universidad Cayetano Heredia	Peru	Role of geographical and environmental variation as risk factors for chronic disease (CVDs and COPD)	3000 individuals, 35 years of age or older, from 4 regions in Peru: Tumbes, Puno (urban), Puno (rural), and Lima	2010	<a href="http://www.cronicas-upch.pe/">http://www.cronicas-upch.pe/</a>

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# Translation and validation of Warmometer, a tool for assessing warmth in patient-provider relationships, for use in Brazilian Portuguese

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## KEY WORDS:

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## ABSTRACT

**BACKGROUND:** Empathy in the patient-provider relationship is associated with important outcomes in healthcare practice. Our aim was to translate and validate Warmometer, a visual tool for assessing warmth in patient-provider relationships, for use in Brazilian Portuguese.

**DESIGN AND SETTING:** Cross-sectional study conducted at an antenatal clinic of a public university hospital in S o Paulo, Brazil.

**METHODS:** The instrument was translated into Brazilian Portuguese and culturally adapted. It was tested for reliability and validity among 32 pregnant women, between June 2015 and January 2016. To assess construct validity, it was correlated with the Consultation and Relational Empathy (CARE) scale (gold standard for patient-provider relationships) and the Interpersonal Reactivity Index (IRI).

**RESULTS:** The translated version of Warmometer had good face and content validity, low intra-observer reproducibility (intraclass correlation coefficient, ICC: 0.224; 95% confidence interval, CI -0.589 to 0.621;  $P = 0.242$ ) and high inter-observer reproducibility (ICC: 0.952; 95% CI 0.902 to 0.977;  $P < 0.001$ ). There was a strong correlation between Warmometer and CARE ( $r = 0.632$ ) and a weak correlation between Warmometer and IRI ( $r = 0.105$ ).

**CONCLUSIONS:** Warmometer was translated, culturally adapted and validated for use in Brazilian Portuguese. The translated version is a reliable tool for assessing the degree of empathy perceived by the patient in a patient-provider relationship.

## INTRODUCTION

Perceived warmth or empathy is defined as a social-emotional ability with affective and cognitive components. These components refer to the ability to share and understand the emotions of others, respectively.<sup>1</sup> Empathy in the patient-provider relationship is associated with important outcomes such as higher patient satisfaction<sup>2</sup> and adherence to treatment,<sup>3</sup> as well as with increased diagnostic accuracy<sup>4</sup> and positive health outcomes.<sup>5,6</sup> During pregnancy, empathy in the patient-provider relationship is associated with satisfaction with delivery.<sup>7</sup>

There are several questionnaires for evaluating empathy in the patient-provider relationship,<sup>8-10</sup> both from the physician's and from the patient's perspective. The Interpersonal Reactivity Index (IRI)<sup>11</sup> and the Consultation and Relational Empathy (CARE) scale<sup>12</sup> are among the ones most used. The IRI is a first-person tool that allows physicians to evaluate themselves, and it was translated into Brazilian Portuguese by Sampaio et al. in 2011.<sup>13</sup> The CARE instrument assesses the patient's perception of empathy in the patient-provider relationship and was translated into Brazilian Portuguese in 2014.<sup>14</sup>

However, written questionnaires can sometimes be difficult to understand and use.<sup>15</sup> Visual tools not only dispense with the need for in-depth reading and writing skills but also spare the participants from many of the barriers associated with completing written questionnaires.

Warmometer is a tool for measuring the warmth of the patient-provider relationship. It is a self-reporting visual and cognitive tool for assessing the socio-emotional quality of healthcare providers from the patient's perspective.<sup>8</sup> This tool was created by Neumann et al. in 2011, in a German hospital specializing in holistic and anthroposophic medicine.

Our objective was to translate, cross-culturally adapt and validate Warmometer for use in Brazilian Portuguese.

## METHODS

### Study design, setting and ethics

This study was approved by the Ethics Committee of the Federal University of São Paulo (CAAE: 20537514.6.0000.5505). All participants signed written informed consent.

First, we translated a 17-item probing questionnaire<sup>8</sup> created to ensure comprehension of Warmometer (Table 1), here referred to as the “probing questionnaire”. Then, we translated Warmometer itself. It was tested for reliability and validity among participants who were pregnant women, between June 2015 and January 2016, according to the procedures described below. To assess construct validity, it was correlated with the Consultation and Relational Empathy (CARE) scale (gold standard for patient-provider relationships) and the Interpersonal Reactivity Index (IRI).

### Participants

For this study, healthy women of any gestational age, who were being managed at the antenatal care clinic of a large public university hospital in the city of São Paulo, Brazil, were recruited between June 2015 and January 2016. Participation was voluntary, and the women had to be at least 18 years of age and be able to speak and read Portuguese fluently. Those with psychiatric diagnoses (e.g. dementia or schizophrenia) were excluded.

Firstly, the principal investigator (MB, an obstetrician) approached the physicians working at the clinic to explain the study and invite them to participate. They were informed that

they would be asked to fill in a questionnaire (the IRI), immediately after conducting a routine antenatal consultation with each participating woman.

The investigator then approached the women immediately after these consultations and told them about the study. Those who fulfilled the selection criteria and agreed to participate received three written questionnaires (a sociodemographic data collection form, a probing cognitive questionnaire and the CARE measurement tool) and also the Warmometer tool, to be answered individually and anonymously in a private room (first interview). The physician who had just examined the participant also received an IRI form to be filled out individually and anonymously. The completed questionnaires were returned to the investigator and were placed in an opaque envelope marked with the participant’s initials.

Two to three weeks later, at the participant’s next scheduled routine antenatal care visit, another investigator (SO, a psychologist) approached the same participants and asked them to again fill out the probing cognitive questionnaire and to respond to the Warmometer tool, individually, in a private room (second interview). The completed questionnaires were placed into each participant’s opaque envelope. As part of their routine antenatal care, all women in this antenatal clinic are cared for by a multidisciplinary team (obstetrician, psychologist, nutritionist, dermatologist, physiotherapist and nurses) and participate in several additional activities (e.g. exercise sessions, group discussions, hydrotherapy, psychotherapy and massage). Since the women remain in the clinic for several hours, the principal investigator (MB) approached them on the same day, two hours later, and repeated the procedures (third interview) that had

**Table 1.** Probing cognitive interview questionnaire<sup>8</sup>

	Probe questions
1	What characteristics and type of behavior demonstrated by your physician is your assessment based on? (see Figure 1, presenting an illustration of the Warmometer)
2	How did you arrive at your answer on the thermometer?
3	How do you perceive the way in which the physician talks to you?
4	What do the gestures of your physician mean to you (e.g. whether your physician shakes your hand to welcome you)?
5	Has your assessment of your physician changed since your first contact with him/her?
6	What do you think about the thermometer as a response format? Would you change anything?
7	Can you please repeat the first question in your own words? What is this question about, in your view?
8	Was the question easy for you to understand? Would you change anything?
9	Please indicate how much warmth your ideal physician would show towards you by placing an “X” directly on the thermometer to the left.
10	What characteristics and type of behavior of an ideal physician is your answer based on?
11	Please imagine a person from your personal environment (e.g. family, friends, neighbors or colleagues) who shows great warmth towards you. Indicate how much warmth this person shows to you by placing an “X” directly on the thermometer to the left.
12	What characteristics and type of behavior is your assessment based on?
13	Please imagine a person from your personal environment (e.g. family, friends, neighbors or colleagues) who shows an average amount of warmth towards you. Indicate how much warmth this person shows you by placing an “X” directly on the thermometer to the left.
14	What characteristics and type of behavior is your assessment based on?
15	Please imagine a person from your personal environment (e.g. family, friends, neighbors or colleagues) who shows coldness towards you. Indicate how much coldness this person shows you by placing an “X” directly on the thermometer to the left.
16	What characteristics and type of behavior is your assessment based on?
17	Do you have any other comments on the issue of human warmth in the patient-provider relationship? Or, is there anything else I should know?

been used by investigator 2 (SO). None of the participants received care from the investigators, at any of their antenatal appointments.

The participants' responses to Warmometer were placed in their individual envelopes. At the end of the study, each of the participants' envelopes contained 3 Warmometer questionnaires; 1 probing cognitive questionnaire with 17 answers (first interview), 2 probing cognitive questionnaires with 4 answers (to questions 9, 11, 13 and 15) obtained in the second and third interviews, the physician IRI questionnaire obtained in the first interview and the sociodemographic data from each participant.

### Details of the questionnaires

#### *The probing cognitive questionnaire*

Based on Tourangeau's model for a cognitive interview questionnaire,<sup>16</sup> Neumann et al.<sup>8</sup> developed a 17-item probing questionnaire to ensure comprehension of Warmometer (Table 1). The original questionnaire used descriptive answers to assess four key points:

1. comprehension of a question;
2. retrieval of information from autobiographical memory;
3. use of heuristic and decision-making processes to estimate an answer; and
4. formulation of a response.

Item 2 was not included in the present study because the participants gave responses to the Warmometer tool immediately after their appointment with the physician, and issues with retrieval of information were thought to be very unlikely.

In the first interview, all participants were asked to answer the full probing cognitive questionnaire before giving responses to the Warmometer tool. In the second and third interviews, the women answered only four of the 17 questions of the probing cognitive questionnaire: degree of warmth of the ideal physician (9); degree of warmth of very warm people (11); degree of warmth of averagely warm people (13); and degree of warmth of cold people (15).

#### *Warmometer*

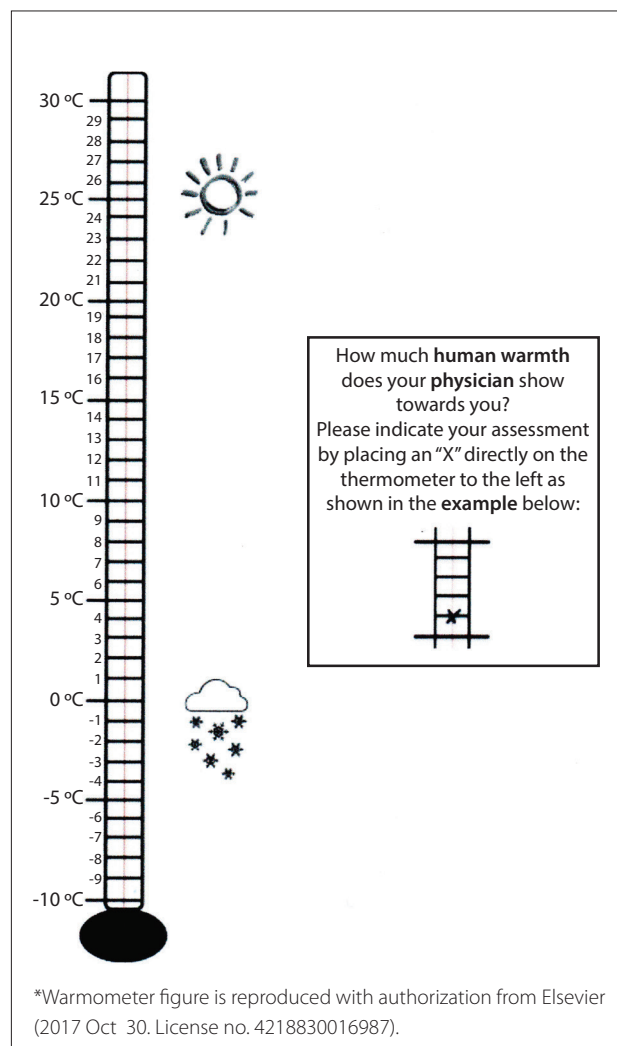
Warmometer provides a short self-reported assessment by patients of physicians' warmth, visually represented by a thermometer. The tool was developed based on the concepts of warmth in human relationships. Neumann et al.<sup>8</sup> considered warmth to be "a higher temperature, a still pleasant feeling, that is no longer cold and not yet hot" and coldness to be the "absence of warmth". To capture differences in individual perceptions of and preferences for warmth and coldness, these authors created an image of a thermometer with a temperature range from -10 °C to +30 °C (Figure 1). They described a "cold patient-provider relationship" as one that was between 15 °C and 18 °C and a "warm patient-provider relationship" as one that was between 22 °C and 24 °C.<sup>8</sup>

### Steps in the cultural adaptation process

#### *The probing cognitive questionnaire*

The original version of the probing cognitive questionnaire (Table 1) was translated from English into Brazilian Portuguese by two native Brazilians who were English teachers. This translation was discussed by the two teachers and the main investigator (MB) until consensus was reached.

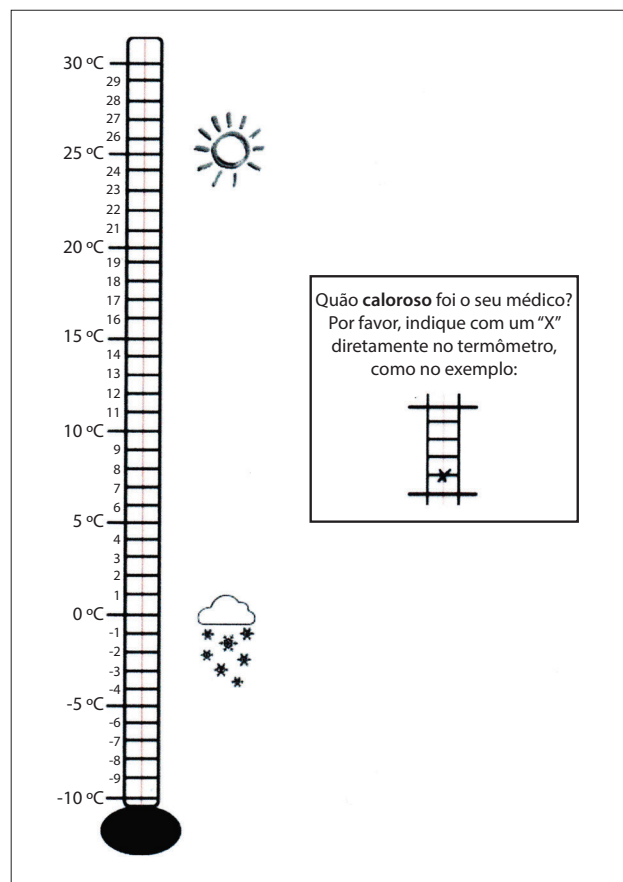
This initial version was tested on 20 pregnant women who were receiving antenatal care in the study clinic. The questions for which more than 15% of the responses consisted of the option "not applicable" were reviewed and modified. This process produced a second version of the probing cognitive questionnaire, which was tested again on the same 20 participants, on another occasion. This version was considered appropriate if less than 15% of the responses to the questions consisted of the option "not applicable".



**Figure 1.** Final version of the Warmometer, as developed by Neumann et al. (2011)<sup>8\*</sup>

### Warmometer

We obtained authorization from the main author of Warmometer (M. Neumann) to translate the instrument into Brazilian Portuguese. The original version of the instrument was translated from English into Brazilian Portuguese in accordance with the methods recommended for translation and cultural adaptation of health-related quality-of-life and self-reporting measurements.<sup>17, 18</sup> Two native Brazilians who were English teachers translated the original text (“How much warmth does your physician show towards you?”) independently. These two versions were discussed by the teachers and the main investigator (MS) until a consensus was reached. The new version was translated back into English by two other Brazilian English teachers and this version was compared with the original English text. The Brazilian Portuguese translation of the Warmometer (Figure 2) was tested on a small group of 20 women to identify any problems of comprehension. The investigators assessed whether the consensus version of the translated Warmometer was appropriately adapted to the linguistic and cultural context of the women who would use the



**Figure 2.** Final version of the Warmometer: translated, culturally adapted and validated for use in Brazilian Portuguese.

instrument, and whether it maintained all the essential characteristics of the original version.

### Assessment of psychometric properties

After translation and cultural adaptation, the final version of Warmometer was tested for reliability and for face, content and construct validity, as detailed below.

Reliability was examined through test-retest procedures in three interviews involving the same participants. In the first interview, 32 participants filled out Warmometer responses. Two to three weeks later, the same participants were approached by two independent investigators at different times (two hours apart) on the same day and were asked to fill out Warmometer responses. We calculated the inter- and intra-test reliability using intraclass correlation coefficients (ICC), with 95% confidence intervals (CI), comparing the individual scores given by the participants in each of the three interviews.

Face validity was determined by reaching a consensus among the investigators involved in translation of the instrument. They evaluated whether the Brazilian version of the Warmometer appeared to measure what it intended to measure.

Content validity refers to how well a test measures the behavior for which it is intended. This needs to be established using a defined standard to compare content or results.<sup>19</sup> Content validity in this study was evaluated by means of checking the answers that were given in the probing cognitive questionnaire that was used to test the participants' comprehension of Warmometer and observed whether the participants had any doubts or queries about answering the questions or any suggestions for changes to the questions.

Construct validity refers to the extent to which the new tool conforms to previous ideas or hypotheses about the concepts (constructs) that are being measured.<sup>19</sup> This was tested by comparing Warmometer with the Consultation and Relational Empathy (CARE) measurement.<sup>12</sup> CARE is a 10-item self-reporting tool for measuring patients' perceptions of relational empathy in consultations, which are evaluated on a Likert scale, ranging from 1 (“poor”) to 5 (“excellent”). Higher scores indicate higher levels of empathy. This tool was translated into Brazilian Portuguese by Scarpellini et al.<sup>14</sup> and has good internal consistency (Cronbach's alpha of 0.867).

The Interpersonal Reactivity Index (IRI),<sup>11</sup> which was filled out by the physicians, was also used to test the construct validity of Warmometer. The IRI is a 28-item self-reporting self-evaluation questionnaire consisting of four seven-item subscales, each of which assesses a specific aspect of empathy: perspective taking (PT) scale; fantasy (FS) scale, including three items of the fantasy-empathy (F-E) scale;<sup>20</sup> empathic concern (EC) scale; and personal distress (PD) scale. Each of these subscales is composed of seven propositions, which are graded by the respondents using a Likert scale, ranging from 1 (“does not describe me well”) to 5

(“describes me very well”). Higher scores indicate higher levels in each of these dimensions, and the sum of the scores of all subscales is used to calculate the overall level of empathy. The IRI was translated into Brazilian Portuguese by Sampaio et al. in 2011 and has good internal consistency (Cronbach’s alpha of 0.861).<sup>13</sup> We used Pearson correlation coefficients to assess the association between the Warmometer scores and the CARE and IRI scores. R values < 0.30, from 0.30 to 0.50 and > 0.50 were interpreted as indicative of weak, moderate and strong correlations, respectively.<sup>21</sup> P-values < 0.05 were considered statistically significant.

We used the Statistical Package for the Social Sciences (SPSS) software, version 21 (IBM Corporation, Armonk, NY, USA), for the statistical analyses.

## RESULTS

We recruited 20 pregnant women for the cultural adaptation of the translations of the probing cognitive questionnaire and Warmometer, and all of the recruited women agreed to participate. The translated version of Warmometer was well understood by all participants. However, over 15% of the women did not understand question 1 of the probing cognitive questionnaire. The translation of this question was then modified, and the revised version of the probing questionnaire was tested again on the same 20 pregnant women. Seventeen women considered that this second version was appropriate.

A total of 40 pregnant women agreed to participate in the validation phase (including the previous 20). Eight were excluded because they returned incomplete questionnaires. Initially, we told all the participants about the importance of the study and that all fields of the questionnaires should be answered. However, to ensure their comfort and confidentiality, the participants were left alone while answering the questionnaires. When we performed the statistical analysis, we needed to compare the responses to Warmometer with the answers given to the other instruments (the 17 items of the probing questionnaire, the Consultation and Relational Empathy (CARE) scale and the IRI. At this stage, we had to exclude 8 women because they did not completely fill in all of these instruments. Thus, a total of 32 women were included in the final analyses. Their mean age was 30.0 years (standard deviation  $\pm$  4.8), ranging from 20 to 41 years. Nearly half of them (47%;  $n = 15$ ) had < 9 years of formal education; 19% ( $n = 6$ ) had 9-12 years; and 34% ( $n = 11$ ) had > 12 years. Most of them (78%;  $n = 25$ ) were white; 1.2% ( $n = 4$ ) were black; and 0.9% ( $n = 3$ ) were of mixed color. Five physicians were invited to participate in the study and filled out IRI questionnaires.

These 32 participants provided the following responses during the first interview (the probing cognitive questionnaire with 17 questions):

- 30 (94%) stated that they would not change anything in the format of the instrument and considered the questions to be “easy to understand”;

- 24 (75%) responded that their assessment was based on the “attention” that they received from the physician;

The following attitudes and behaviors were mentioned by the women as examples of warmth:

- Warmth from their attending physician: attention, tone of voice, eye contact, greeting, smiling and introducing himself/herself;
- Warmth from an ideal physician: being available, calm, happy to be in the consultation, eye contact, showing interest and caring for the patient.

Table 2 presents the mean physician warmth scores (temperatures) according to the participants’ responses to the Warmometer question: “How much warmth does your physician show towards you?” and their answers to questions 9, 11, 13 and 15 (the ones that were responded in the three interviews and are part of Warmometer) of the probing cognitive questionnaire, in the three interviews.

To evaluate test-retest reliability, a total of 32 participants completed the Brazilian Portuguese version of Warmometer three times. The women took an average of 2-3 minutes to answer the questions. There was no significant intra-observer reproducibility, based on the responses obtained by the principal investigator in the first interview and in the second interview 2-3 weeks later, ( $P = 0.491$ ; Pearson correlation coefficient,  $r = 0.126$ ). However, there was significant inter-observer reproducibility, based on correlation of the responses between the second and third interviews (conducted two hours apart by different investigators), ( $P < 0.001$ ,  $r = 0.912$ ).

Homogeneity analysis, using ICC, showed weak intra-observer correlation without statistical significance (ICC: 0.224; 95% confidence interval, CI -0.589 to 0.621;  $P = 0.242$ ) and strong, statistically significant inter-observer correlation (ICC: 0.952; 95% CI 0.902 to 0.977;  $P < 0.001$ ) (Table 3).

**Table 2.** Physician warmth temperatures perceived by 32 pregnant women and responses to probe questions 9, 11, 13 and 15 (see Table 1)

	Mean temperature		
	1 <sup>st</sup> interview <sup>a</sup>	2 <sup>nd</sup> interview <sup>b</sup>	3 <sup>rd</sup> interview <sup>c</sup>
Physician warmth	25.5 $\pm$ 5.6	25.0 $\pm$ 5.9	25.4 $\pm$ 5.5
Ideal physician warmth	27.3 $\pm$ 3.8	26.4 $\pm$ 3.8	25.6 $\pm$ 4.5
Person of great warmth	28.1 $\pm$ 3.2	25.8 $\pm$ 4.1	26.5 $\pm$ 3.9
Person of average warmth	18.8 $\pm$ 6.6	16.9 $\pm$ 6.8	16.8 $\pm$ 6.8
Cold person	3.8 $\pm$ 5.7	7.9 $\pm$ 8.3	6.7 $\pm$ 7.2

<sup>a,b,c</sup>conducted by interviewer 1; <sup>c</sup>conducted by interviewer 2. All values expressed as mean  $\pm$  standard deviation.

## Validity

Almost all participants (94%) stated that Warmometer was easy to understand during the probing questionnaire evaluation, and that they would not change anything in its format or questions. Based on this response, the multidisciplinary team established the face and content validity of the Brazilian Portuguese version of Warmometer.

Construct validity was determined by comparing the Warmometer scores with the CARE and IRI scores in a sample of 32 pregnant women. There was a strong, statistically significant correlation between the Warmometer and CARE scores ( $r = 0.632$ ;  $P < 0.001$ ). There was a weak, statistically insignificant correlation between the Warmometer and IRI scores ( $r = 0.105$ ;  $P = 0.567$ ).

## DISCUSSION

The temperature ratings from Warmometer that our participants gave and their responses to the probing cognitive questionnaire seem to confirm the close relationship between warmth, empathy and social relations. The average temperature ratings given by our participants to their attending physician, in the three interviews, were approximately 25 °C, and this was also very close to the ideal temperature rating for physicians that they gave. This means that they felt welcomed by the attending physician and that the consultations were within their expectations.

Several studies have shown that empathy, or perceived warmth in the patient-provider relationship, is associated with positive health outcomes.<sup>2-6,22</sup> This is especially important during pregnancy, a special period in a woman's life, when a good relationship between the patient and her healthcare providers can promote satisfaction and contribute towards creating good memories of the birth experience.<sup>7</sup> In 2006, Domingues, Santos and Leal<sup>7</sup> conducted a cross-sectional study in a public hospital in Rio de Janeiro, Brazil, to assess the opinions and feelings of 250 women about the care received from healthcare professionals. Nearly 75% of the women (139/187) with a positive perception of their healthcare team reported their delivery experience as good/very good, compared with only 44% (26/59) of those who had a negative perception of their healthcare professionals ( $P < 0.001$ ).

Our pregnant participants stated that they took into consideration not only what the physician said but also the way in

which he/she spoke. "Attention", "tone of voice" and "eye contact" were mentioned by many of our participants as characteristics of warmth in the patient-provider relationship, thus indicating that patients are highly sensitive to nonverbal communication and that this is important to them. According to physiology studies, non-verbal communication is detected more rapidly by the brain (in the amygdala) than is verbal content (in the prefrontal cortex).<sup>23</sup>

In our study, 32 healthy pregnant women gave responses to Warmometer on three different occasions, whereas 16 individuals (8 patients and 8 healthy volunteers) were involved in the development of the original instrument.<sup>8</sup> Our low and statistically insignificant intra-observer ICC score may have been due to the treatment that these women could receive prior to responding to the questionnaire in the clinic (e.g. massage, physiotherapy, psychotherapy or hydrotherapy). In contrast, the inter-observer ICC scores (0.902 to 0.977) and the total ICC score (0.952) were high and statistically significant ( $P < 0.001$ ). This is an interesting finding, since Warmometer was applied by professionals with different backgrounds (an obstetrician and a psychologist), which suggests that the instrument can be used by different types of healthcare professionals.

There was a good correlation between the Brazilian Portuguese Warmometer and the CARE measurement, which is considered to be the gold standard for measuring empathy in patient-provider relationship. However, the CARE questionnaire does so in written form, not visually as in Warmometer. On the other hand, the correlation between the Brazilian Portuguese Warmometer and IRI was not statistically significant ( $P = 0.187$ ). This may have been because Warmometer and IRI assess two different points of view about the empathy of the relationship: respectively, the patient's and the physician's perceptions of warmth. In other words, not all doctors who consider themselves empathic are perceived by patients as being warm. However, contrary to our findings, a Canadian study involving 70 nurses and 70 patients in acute care settings<sup>24</sup> reported that there was a positive correlation between the measurements of nurse-expressed empathy and patient-perceived empathy.

Although empathy receives little attention during medical training or clinical practice, several studies have shown that not only competence but also empathy is critical to improving health outcomes.<sup>2-7,24</sup> Even though the instrument was not developed

**Table 3.** Intra and inter-observer reliability of Warmometer, as assessed in a sample of 32 pregnant women

Warmometer Temperatures	Intraclass correlation			Interclass correlation		
	ICC	95% CI	P-value	ICC	95% CI	P-value
Physician warmth	0.224	-0.589-0.621	0.242	0.952	0.902-0.977	< 0.001
Ideal physician warmth	0.584	0.147-0.797	0.009	0.856	0.705-0.930	< 0.001
Person with great warmth	0.424	-0.180-0.719	0.065	0.908	0.812-0.955	< 0.001
Person of average warmth	-0.136	-1.328-0.445	0.638	0.777	0.543-0.891	< 0.001
Cold person	0.205	-0.629-0.612	0.263	0.727	0.440-0.866	< 0.001

ICC = intraclass correlation coefficient; CI = confidence interval.

specifically for pregnant women, we decided to validate the instrument in this population because we know the importance (both from a theoretical and a practical perspective) of empathy in the patient-provider relationship during pregnancy. This is a special period in a woman's life during which a good relationship between her and the healthcare providers can promote satisfaction and contribute towards creating good memories of the birth experience.<sup>7</sup>

One strong point of this study is that, to the best of our knowledge, this is the first translation of Warmometer to another language. One limitation was that all participants were pregnant women. Therefore, our findings need to be confirmed in future studies involving different populations.

## CONCLUSION

Warmometer was translated, culturally adapted and validated for use in Brazilian Portuguese. This version of the tool has good reliability and validity, and it can be used to assess Brazilian patients' perceptions of warmth among their healthcare providers.

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# Utilization of food outlets and intake of minimally processed and ultra-processed foods among 7 to 14-year-old schoolchildren. A cross-sectional study

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## KEY WORDS:

Child.  
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## ABSTRACT

**BACKGROUND:** Access to food retailers is an environmental determinant that influences what people consume. This study aimed to test the association between the use of food outlets and schoolchildren's intake of minimally processed and ultra-processed foods.

**DESIGN AND SETTING:** This was a cross-sectional study conducted in public and private schools in Florianópolis, state of Santa Catarina, southern Brazil, from September 2012 to June 2013.

**METHODS:** The sample consisted of randomly selected clusters of schoolchildren aged 7 to 14 years, who were attending 30 schools. Parents or guardians provided socioeconomic and demographic data and answered questions about use of food outlets. Dietary intake was surveyed using a dietary recall questionnaire based on the previous day's intake. The foods or food groups were classified according to the level of processing. Negative binomial regression was used for data analysis.

**RESULTS:** We included 2,195 schoolchildren in the study. We found that buying foods from snack bars or fast-food outlets was associated with the intake frequency of ultra-processed foods among 11-14 years old in an adjusted model (incidence rate ratio, IRR: 1.11; 95% confidence interval, CI: 1.01;1.23). Use of butchers was associated with the intake frequency of unprocessed/minimally processed foods among children 11-14 years old in the crude model (IRR: 1.11; 95% CI: 1.01;1.22) and in the adjusted model (IRR: 1.11; 95% CI: 1.06;1.17).

**CONCLUSIONS:** Use of butchers was associated with higher intake of unprocessed/minimally processed foods while use of snack bars or fast-food outlets may have a negative impact on schoolchildren's dietary habits.

## INTRODUCTION

Ultra-processed foods are characterized by high energy density and higher content of free sugars, sodium and total and saturated fat, combined with lower protein and fiber content.<sup>1</sup> They have hyper-palatability, are often offered in large-sized portions and are accompanied by aggressive marketing strategies, which leads to overeating.<sup>2</sup> There is evidence that increased intake of ultra-processed foods and reduced intake of unprocessed or minimally processed foods, and concomitant increases in rates of inactivity, are the factors most strongly associated with obesity and other non-communicable chronic diseases.<sup>3</sup>

In high-income countries, consumption of ultra-processed foods has been widespread for a long time. In middle and low-income countries, there is a rapidly-growing tendency to replace unprocessed and minimally processed foods and meals prepared by traditional culinary methods with commercial ready-to-eat products. This has occurred mainly since the 1980s.<sup>4</sup> The typical dietary intake of Brazilian adolescents is based on excessive consumption of ultra-processed foods.<sup>5</sup>

Changes in eating habits are widely attributed to environmental characteristics that encourage excessive nutritional intake.<sup>6</sup> The current dietary intake and physical activity profile is partially a result of environmental factors, and particularly the features of the built environment,<sup>7</sup> i.e. the environment created by modern societal trends.<sup>8</sup>

Industrialization, urbanization, economic development and globalized markets have created an environment with great availability and accessibility of high levels of energy-dense foods. Furthermore, there is intense social pressure on people to eat these foods.<sup>9</sup>

Residents of communities with easy access to foods that are considered to be healthy tend to have healthier diets.<sup>10</sup> The availability and accessibility of foods that are considered to be either healthier or less healthy are important factors that influence the eating habits of adolescents and adults.<sup>9</sup>

One of the most important environmental determinants influencing people's diets is their degree of access to the establishments that sell food in their neighborhoods.<sup>10</sup> But a significant proportion of studies investigating food environments only evaluate the availability of establishments that sell food and do not consider whether people actually use them.<sup>11</sup>

Given that features of the environment can influence people's nutritional choices, this study aimed to investigate the association between use of food outlets and intake of minimally processed and ultra-processed foods among 7 to 14-year-old schoolchildren.

## METHODS

This was a cross-sectional analytical study conducted in the city of Florianópolis, capital of the state of Santa Catarina, in southern Brazil.

The procedures that were used for sample size calculation and sampling have been described elsewhere.<sup>12</sup> Briefly, we had a possible sample of 2,506 schoolchildren, stratified according to municipal administrative districts, type of school (public or private) and age group (7-10 or 11-14 years). We randomly selected 30 schools (19 public and 11 private schools), and schoolchildren from each school through clusters. Trained researchers collected data between September 2012 and June 2013.

Seven to 14-year-old schoolchildren were recruited after their guardians had signed free and informed consent forms. Individuals with disabilities that prevented assessment and pregnant adolescents were excluded. Socioeconomic, demographic and anthropometric data and information on the dietary intakes and lifestyles of these schoolchildren and their families were acquired through direct measurement or administration of specific data collection instruments, as described below.

The project was approved by the Human Research Ethics Committee at the Federal University of Santa Catarina (no. 120341/2012).

### Socioeconomic and demographic data and use of food outlets

The children's parents received a questionnaire covering socioeconomic and demographic information about the schoolchildren and their families (sex, age and mother's educational level) and data on where they lived and what type of food outlets they used.

Data on food outlets and their use by schoolchildren and their families were obtained through a questionnaire in which the outlets were categorized into eight types: restaurants, snack bars/fast-food outlets, street vendors, supermarkets, mini-markets,

greengrocers/public markets, bakeries and butchers. The children's parents answered "yes" if they frequently used any of the food outlets or "no" if they did not.

Socioeconomic status was estimated based on the average income for the weighting area where the schoolchildren lived (each weighting area comprised a cluster of census tracts).<sup>13</sup> This information was obtained from the 2010 Brazilian demographic census, published by the Brazilian Institute for Geography and Statistics (IBGE).<sup>13</sup> The income values were given in reais (R\$) by IBGE, but for the purposes of this study they were converted into dollars (USD) using the mid-price for the dollar in August 2010 (1 USD = R\$ 1.75), when data collection for the census began.

### Dietary intake assessment and NOVA food classification

Data on dietary intake were obtained from a single dietary recall questionnaire based on the previous day's intake, known as QUADA-3 (Questionário Alimentar do Dia Anterior). This tool was administered at each school, directly to the children, because the tool was developed specifically for children to be able to understand it. It consists of an illustrated questionnaire covering six eating occasions (breakfast, mid-morning snack, lunch, mid-afternoon snack, dinner, and late-evening snack) in chronological order and includes 21 foods or food groups for each eating occasion. This tool was structured as a record in which the frequencies of consumption of different types of food over the previous day were ascertained, but not the quantities.<sup>14</sup>

This questionnaire was given to the schoolchildren and, with help from the researchers, they indicated which foods they had eaten on the previous day at each of these mealtimes. Because the tool was applied within the school setting and there was no school on Saturdays and Sundays, it was not possible to obtain data representing food consumption for Fridays and Saturdays. By giving the questionnaire to the participating schools on alternate school days, we were able to get information on dietary intake on a selection of different days of the week (including Sundays). For the purposes of this study, foods covered by QUADA-3<sup>14</sup> were classified in accordance with the level of processing, as proposed by the NOVA food classification.<sup>4</sup>

The NOVA classification is based on types of food processing, and food groups, according to the extent and purpose of the processing to which they have been subjected.<sup>4</sup> NOVA describes four categories for food classification, according to processing:

1. unprocessed and minimally processed foods;
2. processed culinary ingredients;
3. processed foods; and
4. ultra-processed foods.<sup>4</sup>

Based on the NOVA definitions, the categories were established as described in the following. Unprocessed foods were considered

to be edible parts of animals, plants, fungi or algae that are in the same state as when they were extracted from nature. Minimally processed foods were considered to be unprocessed foods that had been modified through minimal processing after extraction from nature, such as pasteurization, drying, boiling and other processes that do not involve addition of other substances. Processed foods were considered to be those made by adding cooking ingredients to unprocessed and minimally processed foods, for example, fruit and vegetable preserves, salted seeds and smoked meats. Finally, ultra-processed foods were considered to be manufactured preparations containing long lists of ingredients, many of which are utilized exclusively by the industry, such as casein, lactose and hydrogenated fats.<sup>4</sup> Processed cooking ingredients were not included in the categories that were set up, because we were dealing with meals, and not with ingredients (such as salt, sugar, honey, oils and fats).

For the analysis, eight of the 21 foods and food groups investigated using QUADA-3<sup>14</sup> were defined as ultra-processed foods: yoghurt, chocolate milk, “treats” (candies, lollipops, biscuits with fillings and ice cream), potato crisps (US: chips) or chips (US: French fries), sugary soft drinks, pizzas, hamburgers, breads and biscuits. The decision to classify bread as ultra-processed food was justified because our tool was not able to specify what type of bread was consumed and, according to the NOVA classification, breads are ultra-processed if they have other ingredients besides wheat, yeast, water and salt.<sup>4</sup> In this way, we follow the adaptation proposed by Bielemann et al.<sup>15</sup> Twelve foods and food groups were defined as unprocessed or minimally processed foods: vegetables, leafy greens, fruit, fruit juice, rice, beans, pasta, vegetable soup, red meat, chicken, fish and seafood, milk and coffee with milk. The processed foods category was excluded because only one food (cheese) belonged to this group.

### Statistical treatment

The data were processed using EpiData 3.0, with data quality controlled by means of double entry. Statistical analyses were conducted using STATA version 13.0 (StataCorp, Texas, USA), considering the design effect in all analyses.

Data were expressed using absolute and relative frequencies. Associations between exposures (use of each food outlet) and outcomes (the frequencies at which ultra-processed and unprocessed/minimally processed foods were consumed during the previous day) were assessed using negative binomial regression analysis for count data with the presence of excess zeros. Initially, a crude analysis model was constructed. The multivariate model was adjusted for sex, mother’s educational level ( $\leq 8$  years or  $> 8$  years) and the income of the weighting area (expressed in terciles). Stratified analysis was conducted according to age (7-10 or 11-14). A significance level of  $P < 0.05$  was used.

## RESULTS

The characteristics of the study population are shown in **Table 1**. Of the 2,506 schoolchildren, 311 were excluded because lack of an address or its incompleteness prevented their identification. This left 2,195 children (88% of the total sample) available for inclusion. Among the schoolchildren, there were slight majorities of girls (52%), students aged 7-10 years (60%), students enrolled at public schools (61%) and students whose mothers had had at least 8 years of schooling (75%).

**Table 2** shows the absolute and relative frequencies of the schoolchildren’s dietary intake of each type of food, classified as either “unprocessed/minimally processed” or “ultra-processed”. Approximately 99% of the schoolchildren reported that they had eaten both unprocessed/minimally processed foods and ultra-processed foods on the day before the survey. In the unprocessed/minimally processed group of foods, more than half of the children had eaten rice, red meat or chicken, and beans. Among the ultra-processed foods, more than half of the sample had eaten bread or biscuits, sugary soft drinks and chocolate milk.

**Table 3** lists the prevalence of use of food outlets and the association between use of food outlets and intake of ultra-processed foods on the previous day. The food outlets that were most frequented were supermarkets (96.12%), public markets (88.80%) and bakeries (87.76%). We noted that use of snack bars and fast-food outlets had a positive association with intake of ultra-processed foods in the adjusted model among the children aged 11-14 years (incidence rate ratio, IRR: 1.11; 95% confidence interval, CI: 1.01;1.23).

The association between use of food outlets and intake of unprocessed/minimally processed foods is shown in **Table 4**.

**Table 1.** Distribution of sociodemographic characteristics among 7 to 14-year-old schoolchildren. Florianópolis, Brazil, 2012-2013

Sociodemographic characteristics	n (%)
<b>Sex</b>	
Female	1149 (52.3)
Male	1046 (47.7)
<b>Age group (years)</b>	
7-10	1307 (59.5)
11-14	888 (40.5)
<b>Type of school</b>	
Public	1346 (61.3)
Private	849 (38.7)
<b>Mother’s educational level<sup>a</sup></b>	
$\leq$ Completion of primary education ( $\leq 8$ years)	540 (25.3)
$\geq$ Started secondary education ( $> 8$ years)	1595 (74.7)
<b>Income for weighting area (US dollars - USD)*</b>	
3 <sup>rd</sup> tercile (3,022 – 6,165 USD)	669 (30.5)
2 <sup>nd</sup> tercile (2,181 – 3,021 USD)	811 (36.9)
1 <sup>st</sup> tercile (1,395 – 2,180 USD)	715 (32.6)

<sup>a</sup>n = 2,135; \*Conversion from Brazilian Real using the mid-price for the dollar in August 2010 (1 USD = R\$ 1.75).

An association was found between use of butchers and the frequency of intake of unprocessed/minimally processed foods among the children aged 11-14 years in the crude model (IRR: 1.11; 95% CI: 1.01;1.22) and in the adjusted model (IRR: 1.11; 95% CI: 1.06;1.17).

No association was found between use of food outlets and the frequencies of intake of unprocessed/minimally processed foods and ultra-processed foods among the children aged 7-10 years.

## DISCUSSION

Almost all of the schoolchildren interviewed stated that they had eaten ultra-processed foods on the previous day. Eating habits that include excessive consumption of ultra-processed foods are increasing, and this has been attributed to factors such as convenience, simplicity, accessibility and shorter preparation times.<sup>3</sup> Rises in the incomes of Brazilian families, particularly among those in low-income categories, have also been identified as a factor that increases poorer families' access to these products.<sup>16</sup> In association with these factors, ready-to-eat products are marketed aggressively, especially targeting children.<sup>17</sup>

**Table 2.** Dietary intake on previous day, classified according to foods and food groups and their degree of processing, among 7 to 10-year-old and 11 to 14-year-old schoolchildren. Florianópolis, Brazil, 2012-2013

Foods and food groups <sup>a</sup>	Eaten the previous day n (%)	
	7 to 10-year-old schoolchildren	11 to 14-year-old schoolchildren
Unprocessed/minimally processed foods	1,333 (99.5)	840 (98.7)
Rice	999 (74.6)	651 (76.7)
Red meat or chicken	821 (63.0)	604 (70.4)
Beans	848 (63.0)	482 (56.7)
Fruit	688 (51.3)	389 (45.0)
Pasta	664 (48.6)	380 (44.9)
Fruit juice	582 (43.8)	343 (41.5)
Coffee with milk	496 (35.8)	330 (37.2)
Milk	353 (26.1)	209 (23.9)
Vegetables	272 (21.1)	196 (24.3)
Leafy greens	254 (19.9)	204 (24.4)
Vegetable soup	234 (16.2)	57 (6.4)
Fish or seafood	178 (12.4)	97 (10.7)
Ultra-processed foods	1,323 (98.4)	834 (97.6)
Bread or biscuits	1,090 (80.4)	700 (80.9)
Sugary soft drinks	797 (58.8)	497 (59.0)
Chocolate milk	759 (55.9)	422 (49.6)
Treats	603 (45.8)	402 (46.2)
Yoghurt	449 (32.9)	234 (27.2)
Pizzas or hamburgers	328 (23.5)	177 (21.0)
Chips (US: French fries)	255 (17.8)	157 (19.1)
Crisps (US: chips)	235 (16.7)	149 (17.5)

<sup>a</sup>The category identified as "processed food" was excluded because only one food (cheese) belonged to this group.

The dietary intake observed in this study was similar to what has been seen in nationwide studies in Brazil. A study conducted in 2016 among 12 to 17-year-old adolescents found that the most frequently consumed unprocessed/minimally processed foods were rice, beans and beef. Among the ultra-processed foods, bread, biscuits and sugary soft drinks had the greatest prevalence of consumption.<sup>5</sup> Similar dietary behavior was observed by Levy et al.,<sup>18</sup> who found that the most frequently consumed healthy food item was beans, while unhealthy eating was marked by high intake of sugary soft drinks and treats. The share of the Brazilian diet accounted for by ultra-processed products has been growing since the 1980s in metropolitan areas and the same pattern was confirmed in the 2000s, independently of socioeconomic status.<sup>19</sup>

The findings of the present study suggest that there is a positive association between use of snack bars and fast-food outlets and intake of ultra-processed foods. Few studies had explored the relationship between the intake of foods classified according to the level of processing and use of different food outlets.<sup>20,21</sup> Since this subject is relatively new, it is reasonable to compare the present results with those of studies that investigated the availability and density of food outlets and the intake of foods, but not necessarily using classifications according to the level of processing.

A Canadian study reported that living near fast-food outlets had a marked influence on the eating habits of 11 to 15-year-old adolescents. Those in neighborhoods with moderate or high density of fast-food restaurants had an excessive intake of fast food.<sup>22</sup> Similar findings were reported among Danish adolescents of the same age, among whom the boys who had greater exposure to fast-food restaurants in the environs of their schools had higher intake of the foods sold at these establishments than did those who were not exposed to these restaurants.<sup>20</sup>

Another Canadian study on 810 adolescents aged 11 to 14 found that there was poorer quality of diet, with higher intake of fast foods, among those who lived close to or went to schools close to convenience stores and outlets selling fast foods.<sup>23</sup> Similar results were reported by Laska et al.,<sup>24</sup> who found that the sugar-sweetened beverage intake of 349 American adolescents was associated with living close to fast-food restaurants, convenience or grocery stores or any retail facility. Adolescents who lived close to these retailers were also more likely to buy foods from these outlets when their parents or guardians were not around.<sup>24</sup>

Our study showed that there was a positive association between the use of snack bars and fast-food outlets and the intake of ultra-processed foods, when stratified by age, among the adolescents (from 11 to 14 years). Adolescents have more autonomy in relation to purchasing food. In addition to access and autonomy, food choices also reflect an array of personal and social values. Adolescence is an important developmental age accompanied by notable declines in a range of health-related behaviors.<sup>24</sup>

**Table 3.** Association between frequency of ultra-processed food intake and types of food outlet frequented by the family among 7 to 10-year-old and 11 to 14-year-old schoolchildren. Florianópolis, Brazil, 2012-2013

Variables	Use n (%)	Crude model	P-value <sup>a</sup>	Crude model	P-value <sup>a</sup>	Adjusted model	P-value <sup>a</sup>	Adjusted model	P-value <sup>a</sup>
		IRR (95% CI)	7 to 10-year-old schoolchildren	IRR (95% CI)	11 to 14-year-old schoolchildren	IRR (95% CI)	7 to 10-year-old schoolchildren	IRR (95% CI)	11 to 14-year-old schoolchildren
<b>Supermarkets</b>									
No	2,057 (96.12)	1	0.993	1	0.939	1	0.548	1	0.964
Yes		1.00 (0.70;1.45)		0.99 (0.62;1.57)		1.09 (0.73;1.63)		1.01 (0.61;1.65)	
<b>Mini-markets</b>									
No	1,307 (67.83)	1	0.635	1	0.486	1	0.466	1	0.886
Yes		0.98 (0.87;1.10)		1.03 (0.93;1.14)		0.97 (0.87;1.08)		1.01 (0.90;1.12)	
<b>Bakeries</b>									
No	1,785 (87.76)	1	0.470	1	0.806	1	0.566	1	0.693
Yes		1.03 (0.91;1.18)		0.98 (0.73;1.31)		1.03 (0.89;1.20)		0.96 (0.72;1.28)	
<b>Butchers</b>									
No	865 (47.76)	1	0.106	1	0.204	1	0.075	1	0.276
Yes		1.08 (0.97;1.21)		1.08 (0.93;1.26)		1.09 (0.98;1.20)		1.07 (0.91;1.26)	
<b>Public markets</b>									
No	1,839 (88.80)	1	0.865	1	0.540	1	0.956	1	0.631
Yes		0.99 (0.82;1.19)		1.08 (0.75;1.55)		0.99 (0.83;1.19)		1.06 (0.75;1.49)	
<b>Street vendors</b>									
No	1,391 (66.62)	1	0.218	1	0.184	1	0.304	1	0.158
Yes		1.03 (0.97;1.09)		1.06 (0.95;1.17)		1.02 (0.96;1.09)		1.06 (0.96;1.18)	
<b>Snack bars/ fast-food outlets</b>									
No	1,691 (80.26)	1	0.358	1	0.114	1	0.325	1	<b>0.044</b>
Yes		1.05 (0.91;1.21)		1.09 (0.96;1.23)		1.06 (0.91;1.23)		1.11 (1.01;1.23)	
<b>Restaurants</b>									
No	1,772 (83.82)	1	0.282	1	0.323	1	0.066	1	0.473
Yes		1.05 (0.93;1.18)		0.93 (0.78;1.13)		1.08 (0.99;1.18)		0.96 (0.81;1.13)	

<sup>a</sup>Negative binomial regression.

NOTES: Crude model: intake of ultra-processed foods and use of food outlets. Adjusted model: crude model + sex, mother's schooling and income in weighting area. Boldface indicates statistical significance ( $P < 0.05$ ).

**Table 4.** Association between frequency of unprocessed/minimally processed food intake and types of food outlet frequented by the family among 7 to 10-year-old and 11 to 14-year-old schoolchildren. Florianópolis, Brazil, 2012-2013

Variables	Use n (%)	Crude model	P-value <sup>a</sup>	Crude model	P-value <sup>a</sup>	Adjusted model	P-value <sup>a</sup>	Adjusted model	P-value <sup>a</sup>
		IRR (95% CI)	7 to 10-year-old schoolchildren	IRR (95% CI)	11 to 14-year-old schoolchildren	IRR (95% CI)	7 to 10-year-old schoolchildren	IRR (95% CI)	11 to 14-year-old schoolchildren
<b>Supermarkets</b>									
No	2,057 (96.12)	1	0.456	1	0.212	1	0.076	1	0.114
Yes		1.04 (0.89;1.21)		1.14 (0.88;1.49)		1.10 (0.98;1.24)		1.22 (0.91;1.64)	
<b>Mini-markets</b>									
No	1,307 (67.83)	1	0.517	1	0.444	1	0.635	1	0.378
Yes		1.03 (0.90;1.18)		1.07 (0.83;1.39)		1.03 (0.87;1.21)		1.08 (0.86;1.36)	
<b>Bakeries</b>									
No	1,785 (87.76)	1	0.328	1	0.422	1	0.376	1	0.512
Yes		0.94 (0.80;1.11)		1.10 (0.79;1.54)		0.95 (0.80;1.12)		1.09 (0.74;1.61)	
<b>Butchers</b>									
No	865 (47.76)	1	0.225	1	<b>0.040</b>	1	0.261	1	<b>0.006</b>
Yes		1.07 (0.93;1.24)		1.11 (1.01;1.22)		1.08 (0.91;1.27)		1.11(1.06;1.17)	
<b>Public markets</b>									
No	1,839 (88.80)	1	0.865	1	0.728	1	0.760	1	0.846
Yes		0.98 (0.86;1.12)		0.98 (0.81;1.18)		0.99 (0.86;1.13)		0.99 (0.83;1.18)	
<b>Street vendors</b>									
No	1,391 (66.62)	1	0.110	1	0.153	1	0.421	1	0.141
Yes		0.97 (0.95;1.01)		0.95 (0.88;1.03)		0.98 (0.93;1.04)		0.94 (0.85;1.04)	
<b>Snack bars/ fast-food outlets</b>									
No	1,691 (80.26)	1	0.566	1	0.328	1	0.202	1	0.435
Yes		1.01 (0.98;1.03)		0.94 (0.80;1.11)		1.02 (0.98;1.05)		0.94 (0.76;1.16)	
<b>Restaurants</b>									
No	1,772 (83.82)	1	0.318	1	0.688	1	0.292	1	0.517
Yes		1.04 (0.93;1.17)		0.98 (0.82;1.16)		1.05 (0.93;1.18)		0.96 (0.81;1.14)	

<sup>a</sup>Negative binomial regression.

NOTES: Crude model: intake of unprocessed or minimally processed foods and use of food outlets. Adjusted model: crude model + sex, mother's schooling and income in weighting area. Boldface indicates statistical significance ( $P < 0.05$ ).

In the present study, use of butchers was associated with higher intake of unprocessed/minimally processed foods, probably because in this type of establishment, fresh meat that needs culinary preparation is sold. However, use of supermarkets was not associated with intake of unprocessed or minimally processed foods. It needs to be borne in mind that supermarkets sell a wide variety of different food items, ranging from fresh and unprocessed foods to ultra-processed foods.<sup>25</sup>

Living at a greater distance from supermarkets in metropolitan areas reduced the intake of fruits and vegetables among the adult population in a nationwide study in the United States.<sup>26</sup> No associations were observed in another study<sup>23</sup> that was conducted in London among adolescents (11 to 13 years old). A study conducted in the city of Santos (state of São Paulo, Brazil) showed that using supermarkets to purchase fresh products was associated with lower levels of purchases of ultra-processed foods from the supermarket.<sup>21</sup> Another study that was developed among 1,721 children aged 9-10 years, in Norfolk, England, found that higher density of supermarkets was associated not only with higher consumption of fruits and vegetables, but also with more sweets, sugary drinks, breakfast cereals and white bread. Increasing distance from convenience and takeaway food stores was associated with lower intake of crisps, chips, sweets, chocolate and white bread.<sup>27</sup>

The cost of foods and its influence on consumption has also been discussed in the literature. The difference in cost between ultra-processed and minimally processed foods in New Zealand supermarkets was studied by Lutein et al.<sup>28</sup> No statistically significant difference was found in terms of cost, but the authors suggested that ultra-processed products, which made up 83% of the packaged products offered, might have provided time-poor consumers with greater value for money.<sup>28</sup> Swiss researchers examining the driving forces behind increasing consumption of convenience foods identified 15 drivers for purchases of these foods. Among these forces, age, concern for naturalness, nutritional knowledge and cooking skills were the strongest drivers.<sup>29</sup>

## LIMITATIONS

One limitation of this study relates to the dietary intake questionnaire, which assesses frequency of intake rather than quantity (qualitative method). This eliminates difficulties relating to children's assessments of portion sizes and simplifies the memory task through only covering foods eaten the previous day.<sup>30</sup> It is an approach that enables use of a relatively brief questionnaire that is easy for children to answer with minimal assistance.<sup>14</sup> However, one day's dietary intake may not be representative of habitual individual intakes. On the other hand, our results are made more robust by the reasonable sample size and the good coverage of different days of the week, including weekdays and

Sundays.<sup>14</sup> Additionally, we recognize that not every type of food purchased from each type of outlet was evaluated.

The strengths of our study were the sample size and the adjustment of the data for sociodemographic and economic control variables. Classification of foods according to degree of processing introduces additional evidence to help explain the global epidemic of non-communicable chronic diseases, including obesity among children and adolescents,<sup>31</sup> considering that classification of foods according to nutritional categories alone has not explained this relationship.<sup>3</sup>

Many different studies have investigated the availability and presence of food outlets and dietary intake among children and adolescents.<sup>32,33</sup> In the present study, parents and their children were asked whether they actually used these establishments, without attempting to identify whether they were located in the vicinities of their schools/homes. Research conducted by Leite et al.<sup>34</sup> observed that food retailers that mostly sold ultra-processed foods were significantly closer to schools than were those that mostly sold foods with lesser degrees of processing, thus demonstrating the importance of also investigating retailers close to schools.

## CONCLUSION

The results suggest that use of butchers contributed towards increasing the intake of unprocessed/minimally processed foods, thus showing the importance of the choices of places to buy foods. In contrast, schoolchildren's use of snack bars and fast-food outlets was related to their intake of ultra-processed foods, and this negatively influenced their dietary habits. Future studies should incorporate other features of the environment that influence dietary intake and choices. In addition, mapping of retail food outlets in specific environments could facilitate development of ways to promote healthy eating that are suitable for specific populations and the environments in which they live. Public health actions should address food labeling to make it easier for consumers to understand what they are buying. A means to help direct people towards places that sell fresh and healthy foods so that they avoid outlets for ultra-processed foods is also needed.

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# Dietary intake of non-dialysis chronic kidney disease patients: the PROGREDIR study. A cross-sectional study

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## KEY WORDS:

Renal insufficiency, chronic.  
Diet.  
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## ABSTRACT

**BACKGROUND:** Despite evidence that diet is very important in relation to chronic kidney disease (CKD) progression, studies in this field are scarce and have focused only on some specific nutrients. We evaluated the energy, macronutrient and micronutrient intakes and dietary patterns of non-dialysis CKD participants in the PROGREDIR study.

**DESIGN AND SETTING:** Cross-sectional study; CKD cohort, São Paulo, Brazil.

**METHODS:** Baseline data on 454 participants in the PROGREDIR study were analyzed. Dietary intake was evaluated through a food frequency questionnaire. Dietary patterns were derived through principal component analysis. Energy and protein intakes were compared with National Kidney Foundation recommendations. Linear regression analysis was performed between energy and nutrient intakes and estimated glomerular filtration rate (eGFR), and between sociodemographic and clinical variables and dietary patterns.

**RESULTS:** Median energy and protein intakes were 25.0 kcal/kg and 1.1 g/kg, respectively. In linear regression, protein intake ( $\beta = -3.67$ ;  $P = 0.07$ ) was related to eGFR. Three dietary patterns (snack, mixed and traditional) were retained. The snack pattern was directly associated with male gender ( $\beta = 0.27$ ;  $P = 0.006$ ) and inversely with diabetes ( $\beta = -0.23$ ;  $P = 0.02$ ). The traditional pattern was directly associated with male gender ( $\beta = 0.27$ ;  $P = 0.007$ ) and schooling ( $\beta = 0.40$ ;  $P < 0.001$ ) and inversely with age ( $\beta = -0.01$ ;  $P = 0.001$ ) and hypertension ( $\beta = -0.34$ ;  $P = 0.05$ ).

**CONCLUSIONS:** We identified low energy and high protein intake in this population. Protein intake was inversely related to eGFR. Dietary patterns were associated with age, gender, schooling level, hypertension and diabetes.

## INTRODUCTION

Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73m<sup>2</sup> or persistent albuminuria, affects more than 10% of the world's population.<sup>1,2</sup> Early diagnosis of CKD is important for reducing the risk of progression and cardiovascular morbidity and mortality, which is 30 times greater among people with CKD than in the general population.<sup>3</sup> Management of modifiable risk factors is essential, and diet has emerged as an important but often neglected therapeutic tool for prevention and retardation of CKD progression.<sup>4</sup>

Currently, the main goals of nutritional therapy in relation to CKD are to reduce accumulation of byproducts from metabolism and reduce progression of renal disease.<sup>5</sup> In addition, diet may form a strategy for preventing or ameliorating complications of CKD, including acidosis, hyperkalemia, hyperphosphatemia, uremic symptoms, bone diseases and protein-energy wasting.<sup>6,7</sup> However, diet is still underused as a prevention strategy.<sup>8</sup> Furthermore, although low-protein diets are the strategies that have been most studied in relation to CKD, there is evidence to suggest that many other nutrients may influence renal outcomes,<sup>4</sup> such as phosphorus, sodium, potassium, calcium and vitamin K. In addition, few studies have addressed new analytical approaches, such as dietary pattern analysis, rather than evaluation of individual nutrients.<sup>7</sup>

PROGREDIR is a cohort study that was designed to evaluate the determinants of CKD progression and mortality risk among CKD patients.<sup>9</sup> The cohort essentially comprises people with CKD classes 3 and 4 living in São Paulo, Brazil, and diet is one of the factors under investigation.

## OBJECTIVE

We evaluated the association between energy, macronutrient and micronutrient intakes and eGFR, along with dietary patterns and their associated factors among the participants of the PROGREDIR study.

## METHODS

The present study consisted of an evaluation on baseline data from the PROGREDIR study. Details of the methods have been published elsewhere.<sup>9</sup> Briefly, patients attending the outpatient service of Hospital das Clínicas, São Paulo, a quaternary-level care facility, were invited to participate in the study. Initially, from the outpatient records, all patients aged  $\geq 30$  years old who presented at least two creatinine measurements (with a minimum interval of three months)  $\geq 1.6$  mg/dl for men and  $\geq 1.4$  mg/dl for women were considered to be potential candidates. Patients who were attending oncology, psychiatry, urology, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), viral hepatitis and glomerulonephritis services were excluded. The remaining candidates were then contacted by phone and invited to participate if none of the following exclusion criteria were met: hospitalization or acute myocardial infarction in the last six months, autoimmune diseases, pregnancy, psychiatric diseases, ongoing chemo or immunosuppressive therapy, ongoing renal replacement therapy, glomerulonephritis, HIV/AIDS infection, hepatitis B or C, or previous transplantation of any organ. Recruitment took place from March 2012 to December 2013, and 454 participants were enrolled. The study was approved by two local ethics committees, and written informed consent was obtained from all participants (protocol number 11147/11, approved on November 4, 2011, and protocol number 0798/11, approved on February 2, 2012).

Each participant visited the research center for interviews and clinical examinations in accordance with standard protocols. The interviews and clinical examinations were conducted by trained personal under strict quality control conditions. Data on sociodemographic variables (age, gender, schooling level and income class) and lifestyle variables (tobacco use, alcohol use and physical activity practice) were self-reported. Diabetes was defined using a five-criterion definition that included any previous medical history of diabetes, use of medication to treat diabetes, fasting plasma glucose  $\geq 126$  mg/dl, glycated hemoglobin  $\geq 6.5\%$ , and two-hour plasma glucose  $\geq 200$  mg/dl (oral glucose tolerance test). eGFR was estimated by means of the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>10</sup>

We used the validated food frequency questionnaire (FFQ) of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)<sup>11</sup> to evaluate the dietary intake. The questionnaire asked about 114 foods or preparations and evaluated the frequency (daily, weekly

or monthly) and the usual amount of intake of each food/preparation (in household measurements). In addition, it also included 19 questions about the characteristics of the subjects' dietary habits over the last 12 months. This FFQ was applied by staff who had been trained for this function. After data collection, the FFQ was reviewed to verify whether the portion size of the foods was in accordance with what is usually consumed by the Brazilian population.

To evaluate energy and nutrient intakes, we used the United States Department of Agriculture (USDA) Food Composition Databases<sup>12</sup> except when these values were outside of the range of 80% to 120% of the values in the Brazilian Table of Food Composition,<sup>13</sup> in which case we used the latter values. We excluded patients whose energy intake was higher than 5,000 kcal ( $n = 11$ ) from the analyses, because these are unlikely values that might have led to overestimation of nutrient intakes.<sup>14</sup>

Macronutrient and micronutrient intakes were adjusted for energy using the residual method.<sup>15</sup> To analyze energy and protein intake per kg, we used the current body weight, or an adjusted weight when body mass index adequacy was less than 95% or greater than 115%.<sup>16</sup> The energy and protein intakes were compared with the National Kidney Foundation recommendations.<sup>16</sup> Intakes of supplements and medications were not taken into consideration in the current analyses.

Dietary patterns were derived from principal component analysis, with orthogonal (varimax) rotation to extract factors. We considered the daily frequency of intake of each food in the analyses. Subsequently, foods with similar nutritional compositions were grouped into 20 foods/food groups. An exploratory factor analysis was performed, and the adequacy of the data was evaluated by means of the Kaiser-Meyer-Olkin (KMO) test and the Bartlett test of sphericity (BTS). We set different numbers of factors and chose those with interpretable patterns, which were named according to the interpretation of the data. A score was determined for each pattern, which allowed each participant to have one factor score for all patterns identified.<sup>17</sup>

Energy and nutrient intakes were presented as means and standard deviations or as medians and interquartile ranges, according to gender. The variables were tested for normal distribution using the Kolmogorov-Smirnov test, and then differences between the groups were tested using Student's t test (normal distribution) or the Mann-Whitney test (non-normal distribution). Linear regression analysis was performed between energy and nutrient intakes and eGFR as a dependent variable and between sociodemographic and clinical variables and dietary patterns (factor scores) as a dependent variable. All analyses were performed using the SPSS software, version 17.0.

## RESULTS

The baseline characteristics of the participants included in the study are described in **Table 1**. There was a predominance of

elderly, male, hypertensive and diabetic participants. The mean eGFR was  $38.4 \pm 14.6$  (ml/min/1.73 m<sup>2</sup>).

Regarding energy and nutrient intakes, 293 (66.1%) of the participants showed an energy intake below the recommended amount, while 399 (90.1%) of them had a protein intake above the recommended amount for non-dialysis CKD patients. The male patients presented statistically higher intakes of energy (kcal) and iron than those of the females, who presented higher intake of protein (g/kg), dietary fiber, vitamin A, vitamin E, thiamine, pantothenic acid, cobalamin, vitamin C and potassium (Table 2).

In the univariate linear regression analysis, protein intake (g/kg) was inversely related to eGFR, while pyridoxine intake was directly associated. After adjustment for age, gender, diabetes, microalbuminuria and systolic blood pressure, only protein intake (g/kg) showed a trend towards remaining inversely related to eGFR (Table 3).

Three dietary patterns were retained for subsequent analysis. The snack pattern was composed predominantly of breads, biscuits, cakes, farinaceous products, butter, margarine, eggs, processed

meat, sweets, snacks, whole dairy products and sweetened beverages, which explained 12.6% of the variance. The mixed pattern was composed of whole grains, pasta, tubers, red meat, poultry, fish, seafood, fruits, vegetables, low-fat dairy products and natural juice, which explained 8.9% of the variance. The traditional pattern was composed of white rice, beans and coffee, which explained 7.0% of the variance. These patterns are shown in Table 4. The value from the KMO test was 0.601 and the P-value of the BTS was < 0.001.

The snack pattern was directly associated with male gender and inversely related to diabetes. The traditional pattern was directly associated with male gender and schooling level and inversely related to age and hypertension (Table 5). None of the patterns was significantly related to eGFR.

## DISCUSSION

In the present study, the participants reported having low energy and high protein intakes in relation to the nutritional recommendations for CKD patients. This is noteworthy, considering that this population was recruited from outpatient services in one of the major public hospitals in São Paulo. This finding is

**Table 1.** Baseline characteristics of participants in the PROGREDIR study

Variable*	All n = 454	Male n = 287	Female n = 167	P†
<b>Sociodemographic variables</b>				
Age, years	68 (60-76)	68 (61-76)	69 (59-77)	0.49
Schooling ( $\leq$ 8 years of study), n (%)	287 (63.2)	167 (58.2)	120 (71.9)	0.004
Lower middle class, n (%)	248 (54.6)	142 (49.5)	106 (63.5)	0.004
<b>Lifestyle variables</b>				
Tobacco use, n (%)	41 (9.0)	27 (9.5)	14 (8.4)	< 0.001
Alcohol use, n (%)	171 (37.7)	132 (46.2)	39 (23.4)	< 0.001
Physical activity practice, n (%)	137 (30.2)	104 (36.9)	33 (20.0)	< 0.001
<b>Clinical and laboratory variables</b>				
Hypertension, n (%)	416 (91.6)	262 (91.3)	154 (92.2)	0.73
Diabetes, n (%)	257 (56.6)	167 (58.2)	90 (53.9)	0.37
eGFR, ml/min/1.73 m <sup>2</sup>	$38.4 \pm 14.6$	$40.4 \pm 15.4$	$34.8 \pm 12.4$	< 0.001
Serum urea, mg/dl	69 (54-89)	69 (54-87)	70 (55-93)	0.33
Microalbuminuria, mg/g creatinine	83 (15-668)	70 (14-619)	94 (21-813)	0.32
Serum phosphorus, mg/dl	$3.6 \pm 0.6$	$3.6 \pm 0.6$	$3.8 \pm 0.6$	< 0.001
Serum potassium, mEq/l	$4.6 \pm 0.5$	$4.6 \pm 0.5$	$4.5 \pm 0.5$	0.25
Glycated hemoglobin, %	6.2 (5.8-7.2)	6.2 (5.7-7.2)	6.2 (5.9-7.2)	0.59
Total cholesterol, mg/dl	166 (140-191)	157 (133-180)	179 (159-209)	< 0.001
LDL-C, mg/dl	88 (68-109)	81 (63-105)	94 (75-124)	< 0.001
HDL-C, mg/dl	44 (37-53)	41 (34-48)	49 (42-58)	< 0.001
Triglycerides, mg/dl	142 (99-193)	142 (99-188)	140 (97-202)	0.57
Systolic blood pressure, mmHg	$140 \pm 24$	$139 \pm 24$	$142 \pm 25$	0.19
Diastolic blood pressure, mmHg	75 (67-84)	75 (67-85)	75 (67-82)	0.55
<b>Anthropometric measurements</b>				
Body mass index, kg/m <sup>2</sup>	29 (26-32)	29 (26-32)	29 (25-33)	0.66
Body fat, %	30 (27-34)	28 (26-31)	35 (32-40)	< 0.001

\*Continuous variables: mean  $\pm$  standard deviation or median (with interquartile range); categorical variables: number (with percentage); †P-value for comparison between gender groups.

eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein; LDL-C = low-density lipoprotein.

concordant with data from other studies that have also reported low energy and high protein intake among non-dialysis CKD patients, and it highlights the difficulty in achieving efficacious application of nutritional guidelines in cases of chronic diseases. In a study by Avesani et al.,<sup>18</sup> an energy intake of 22.4 kcal/kg was identified among Brazilian patients, which was lower than what was observed in the present study. The energy and protein intake of the sample of the present study was similar to that found in the Modification of Diet in Renal Disease (MDRD) study, in an American population with CKD, but was higher than what was found in the Chronic Renal Insufficiency Cohort (CRIC) study and the National Health and Nutrition Examination Survey (NHANES III) study.<sup>19</sup>

Although a low-protein diet is currently the main therapeutic dietary recommendation for CKD, its actual application in clinical settings varies widely. Several factors may be contributing towards this, such as difficulty in establishing multidisciplinary approaches, lack of adoption of low-protein diets, fear of intensification of protein-energy wasting and low adherence to treatment by patients.<sup>20</sup> Nonetheless, it was surprising to observe that

90% of the CKD population in the PROGREDIR study reported having a protein intake above the recommended value. There may have been several reasons for this, and these were not evaluated in the present study, but they possibly include the dietary habits of the Brazilian population, which are known to include high animal protein intake,<sup>21</sup> along with low adherence to treatment and lack of use of dietary interventions as an important tool for medical treatment. These results show that implementation of low-protein

**Table 3.** Linear regression between nutrient intakes and eGFR among participants in the PROGREDIR study

Variable	$\beta$	95% CI	P
<b>Model 1 - Univariate regression</b>			
Protein, g/kg	-6.26	-10.10- -2.41	0.001
Pyridoxine, mg	4.52	0.18-8.86	0.04
<b>Model 2 - Variables adjusted for age, gender, diabetes, microalbuminuria and systolic blood pressure</b>			
Protein, g/kg	-3.67	-7.60-0.26	0.07
Pyridoxine, mg	2.68	-1.53-6.88	0.21

Dependent variable: eGFR = estimated glomerular filtration rate; CI = confidence interval.

**Table 2.** Energy and nutrient intakes among all participants in the PROGREDIR study and according to gender

Energy/Nutrient*	Intake <sup>†</sup>			P <sup>‡</sup>
	All n = 443	Male n = 277	Female n = 166	
Energy, kcal	1923 (1491-2489)	2105 (1611-2684)	1625 (1286-2152)	< 0.001
Energy, kcal/kg	25.0 (19.5-33.0)	26.3 (19.9-34.0)	24.3 (19.1-31.6)	0.10
Protein, g	83 (72-97)	83 (73-96)	83 (72-98)	0.73
Protein, g/kg	1.1 (0.9-1.4)	1.0 (0.9-1.2)	1.3 (1.0-1.5)	< 0.001
Carbohydrate, g	289 ± 41	288 ± 44	290 ± 37	0.49
Total fat, g	50 ± 11	51 ± 11	49 ± 10	0.14
Dietary fiber, g	26.2 ± 8.5	25.4 ± 8.3	27.5 ± 8.6	0.01
Vitamin A, µg RAE	328 (236-505)	321 (231-480)	354 (253-587)	0.02
Vitamin E, mg	6.4 (5.2-7.9)	6.1 (5.0-7.5)	6.9 (5.7-8.5)	< 0.001
Vitamin K, µg	160 (106-249)	160 (102-246)	160 (108-260)	0.44
Thiamine, mg	1.3 (1.0-1.8)	1.2 (1.0-1.6)	1.4 (1.0-2.1)	0.001
Riboflavin, mg	1.3 (0.9-1.8)	1.3 (0.9-1.8)	1.4 (0.9-1.8)	0.77
Niacin, mg	20.8 (15.0-31.1)	21.1 (15.4-30.4)	20.5 (14.7-34.1)	0.86
Pyridoxine, mg	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.34
Folate, µg	520 (447-608)	523 (439-611)	513 (453-603)	0.95
Cobalamin, µg	3.7 (2.8-4.8)	3.6 (2.7-4.7)	4.1 (3.0-5.3)	0.004
Vitamin C, mg	151 (74-261)	135 (65-221)	193 (104-311)	< 0.001
Magnesium, mg	276 (240-329)	274 (240-318)	284 (242-342)	0.15
Manganese, mg	2.9 (2.4-3.5)	2.8 (2.4-3.4)	3.0 (2.4-3.6)	0.24
Calcium, mg	737 (539-974)	714 (533-959)	787 (549-990)	0.11
Iron, mg	10.2 ± 2.4	10.4 ± 2.4	9.9 ± 2.4	0.04
Zinc, mg	9.7 (8.4-11.8)	9.9 (8.6-11.8)	9.5 (8.0-11.8)	0.09
Selenium, µg	120 (104-139)	119 (102-136)	120 (106-142)	0.24
Phosphorus, mg	1184 ± 232	1178 ± 223	1196 ± 247	0.43
Sodium, mg	2236 (1868-2547)	2217 (1866-2613)	2241 (1875-2468)	0.57
Potassium, mg	3044 ± 700	2985 ± 681	3143 ± 720	0.02

\*Nutrient intakes after adjustment for energy, by means of residual method; <sup>†</sup>mean ± standard deviation or median (with interquartile range); <sup>‡</sup>P-value for comparison between gender groups. RAE = retinol activity equivalent.

diets is not being accomplished in this CKD population, despite the fact that these individuals mostly presented CKD of classes 3 and 4 and were at high risk of CKD progression.

In addition, in the present study, protein intake showed a strong trend towards being inversely associated with eGFR in the linear regression analysis. Although we cannot address causality in this cross-sectional study, this finding is concordant with data from other studies that have suggested that protein intake is

associated with CKD progression. These studies form the basis for the dietary recommendation of lowering protein intake to less than 0.8 g/kg/day.<sup>16</sup>

The low energy intake in this population may have been due to several factors, such as anorexia, nausea, anemia, restrictive diets and comorbidities. Low energy intake is one of the factors associated with the development of protein-energy wasting,<sup>22</sup> which is related to increased morbidity and mortality in CKD cases.<sup>23</sup>

**Table 4.** Distribution of factor loadings of dietary patterns identified among participants in the PROGREDIR study

Food or food group	Dietary pattern		
	Snack	Mixed	Traditional
White rice	-0.058	0.232	<b>0.809</b>
Breads, biscuits, cakes and farinaceous products	<b>0.586</b>	0.099	0.154
Whole grains	-0.146	<b>0.300</b>	-0.597
Pasta and tubers	0.146	<b>0.358</b>	0.144
Butter and margarine	<b>0.521</b>	0.133	0.027
Eggs	<b>0.341</b>	0.308	0.115
Red meat	0.190	<b>0.315</b>	0.087
Processed meat (sausages, hamburgers, ham, mortadella, bacon, canned sardines)	<b>0.558</b>	0.160	0.037
Poultry	0.105	<b>0.427</b>	0.000
Fish and seafood	-0.029	<b>0.440</b>	-0.030
Beans (beans, <i>feijoada</i> , lentil, chickpeas, peas)	-0.003	0.276	<b>0.613</b>
Fruits	0.178	<b>0.552</b>	-0.196
Vegetables	-0.047	<b>0.658</b>	0.101
Sweets (ice cream, candies, gelatin, chocolate, pudding, fruit jam, honey)	<b>0.437</b>	0.106	-0.155
Snacks ( <i>pão de queijo</i> , pizza, <i>esfiha</i> , <i>pastel</i> , <i>coxinha</i> , hot dog, popcorn)	<b>0.237</b>	0.123	0.028
Coffee	0.245	-0.005	<b>0.277</b>
Whole dairy products	<b>0.609</b>	-0.086	0.023
Low-fat dairy products	-0.222	<b>0.374</b>	-0.375
Natural juice	0.078	<b>0.323</b>	0.029
Sweetened beverages (soda, fruit nectar)	<b>0.504</b>	-0.162	0.238
% of variance explained	12.6	8.9	7.0
Cumulative % of variance	12.6	21.5	28.5

Values in bold indicate greater adherence of a food or food group to the dietary pattern.

**Table 5.** Linear regression between sociodemographic and clinical variables and the dietary patterns among participants in the PROGREDIR study

Variable	Dietary pattern					
	Snack		Mixed		Traditional	
	$\beta$	P	$\beta$	P	$\beta$	P
<b>Model 1 - Univariate regression</b>						
Age, years	0.002	0.55	0.002	0.60	-0.01	0.001
Male gender	0.27	0.006	-0.05	0.61	0.27	0.007
Schooling level ( $\leq 8$ years of study)	0.01	0.91	-0.11	0.25	0.23	0.02
Hypertension	0.08	0.66	-0.13	0.45	-0.40	0.03
Diabetes	-0.22	0.03	0.17	0.08	-0.12	0.20
eGFR, ml/min/1.73 m <sup>2</sup>	0.003	0.29	0.001	0.73	0.006	0.08
BMI, kg/m <sup>2</sup>	-0.01	0.28	-0.02	0.06	0.002	0.86
<b>Model 2 - Variables adjusted for age and gender</b>						
Schooling level ( $\leq 8$ years of study)	0.02	0.83	-0.16	0.11	0.40	< 0.001
Hypertension	0.06	0.76	-0.16	0.38	-0.34	0.05
Diabetes	-0.23	0.02	0.15	0.11	-0.13	0.18
eGFR, ml/min/1.73 m <sup>2</sup>	0.002	0.49	0.002	0.62	0.002	0.47
BMI, kg/m <sup>2</sup>	-0.007	0.47	-0.02	0.09	-0.002	0.81

Dependent variables: factor scores for each dietary pattern. BMI = body mass index; eGFR = estimated glomerular filtration rate.

Although it has been shown that low energy intake is related to lower eGFR and higher serum creatinine and blood urea nitrogen,<sup>24</sup> our study did not show any significant relationship between eGFR and energy intake.

There is a lack of Brazilian studies evaluating the micronutrient intakes of non-dialysis CKD patients. In a study that evaluated the zinc and iron content in the diets of Brazilian non-dialysis CKD patients, low content of these minerals in comparison with those of the present study were observed.<sup>25</sup> We were unable to identify any other Brazilian studies evaluating the micronutrient intakes of non-dialysis CKD patients.

In a study conducted in Poland that evaluated the dietary intake of non-dialysis female CKD patients by means of a three-day food record, the intake was lower than in the present study for all micronutrients except for vitamin A, vitamin E and pyridoxine.<sup>26</sup> In three large American cohort studies (MDRD, CRIC and NHANES III), high phosphorus intake was observed,<sup>19</sup> as in the present study, in which an amount of 1184 mg was recorded, i.e. almost 60% above the recommended amount.<sup>27</sup> However, in the present study, the sodium intake was lower than in those studies and the potassium intake was slightly higher.<sup>19</sup>

The dietary patterns identified in the present study were similar to those of other studies conducted among with Brazilian adults and elderly people with normal eGFR.<sup>28-30</sup> According to the value found in the KMO test and the P-value of the BTS, the factor analysis can be considered adequate.<sup>31</sup> In addition, the accumulated variance was similar to that of other studies.<sup>28,32</sup>

We emphasize that the mixed pattern, composed of whole grains, meats, fruits and vegetables is generally referred to as “healthy” or “prudent” in studies on dietary patterns.<sup>28,30,33</sup> However, because a low-protein diet is recommended for non-dialysis CKD patients, we consider that high intake of meats, and consequently protein, may not be healthy or prudent in this population, and thus we name this pattern “mixed.”

The traditional pattern was directly associated with male gender and inversely associated with age, as found by Cardoso et al.<sup>34</sup> in a population study. Male gender was also associated with the snack pattern, as verified by Ferreira et al.,<sup>32</sup> which may indicate a minor concern regarding feeding among men. The snack pattern was inversely associated with presence of diabetes, which may suggest that the diabetic subjects altered their dietary pattern because of their disease, which may explain why the diabetics consumed higher amounts of protein, vitamins and minerals than did the non-diabetic participants (data not shown).

In our study, none of the dietary patterns were associated with eGFR. In accordance with this finding, Gutiérrez et al.<sup>35</sup> showed in a cohort study that no dietary pattern was related to CKD progression. However, a diet rich in fruits and vegetables was associated with lower risk of mortality. In addition, in a recent

meta-analysis, there was no association between a healthy pattern (higher in fruits, vegetables, fish, cereals and whole grains and lower in red meat and refined sugars) and the risk of end-stage renal disease, but it was found that this pattern was associated with lower risk of mortality.<sup>36</sup>

In studies that included participants without baseline kidney disease, the results have been different. In a subgroup analysis from the Nurses' Health Study, the Western pattern (rich in red and processed meats, saturated fats and sweets) was directly related to decreased eGFR and microalbuminuria, while the DASH (Dietary Approaches to Stop Hypertension) pattern was inversely associated with decreased eGFR.<sup>37</sup> In the ULSAM (Uppsala Longitudinal Study of Adult Men) cohort, higher adherence to the Mediterranean diet was associated with lower presence of CKD and higher survival rates.<sup>38</sup>

These results may indicate that dietary patterns have less influence on the risk of end-stage renal disease after CKD has already become established and has reached moderate to advanced stages. However, higher intake of fruits and vegetables appears to be beneficial in relation to the risk of mortality among people with impaired and normal kidney function. Further studies may confirm these findings and also evaluate the association between dietary patterns and other factors, such as cardiovascular risk.

Our study had some limitations. Firstly, it was a cross-sectional analysis. Secondly, the PROGREDIR population is a hospital-derived sample, which implies that the diet reported was possibly influenced by current illnesses and their treatments. This may have reduced the extent to which the dietary assessment reflected the long-term previous intake. Furthermore, FFQs are limited instruments that may not include all foods consumed, which therefore may impair quantification of nutrient intakes. The participants who could have underreported their energy intake were not excluded from the analyses. However, we used the residual method to adjust the intake of all nutrients by energy, obtaining the intake data without the influence of energy.<sup>15</sup> Despite these limitations, the study included a representative sample and used an appropriate method of analysis. Hence, it showed interesting results regarding the dietary profile and patterns of a CKD population.

## CONCLUSION

We found low energy intake and high protein intake in a CKD population, thus demonstrating the need for nutritional intervention. In addition, protein intake was inversely related to eGFR. Dietary patterns were not associated with eGFR, but were associated with age, gender, schooling level and presence of hypertension and diabetes, thus suggesting that sociodemographic and clinical factors are associated with dietary intake and should be considered in nutritional interventions.

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# Pneumo-phono-articulatory coordination assessment in dysarthria cases: a cross-sectional study


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## KEY WORDS:

Dysarthria.  
Speech disorders.  
Respiration.  
Speech production measurement.  
Neurology.

## ABSTRACT

**BACKGROUND:** Pneumo-phono-articulatory coordination is often impaired in dysarthric patients. Because all speech is produced upon exhalation, adequate respiratory support and coordination are essential for communication. Nevertheless, studies investigating respiratory parameters for speech are scarce. The objectives of the present study were to analyze and compare the numbers of words and syllables (universal measurement) per exhalation among healthy and dysarthric speakers, in different speech tasks.

**DESIGN AND SETTING:** A cross-sectional analytical study with a control group was conducted at the Department of Speech, Language and Hearing Sciences at UNIFESP.

**METHODS:** The study sample consisted of 62 individuals: 31 dysarthric patients and 31 healthy individuals matched for sex, age and education level. All participants performed number counting and text reading tests in which the numbers of words and syllables per exhalation were recorded. All measurements obtained from the two groups were compared.

**RESULTS:** Statistically significant differences between the dysarthric and healthy groups were found in the two tasks (counting of syllables and words per exhalation) ( $P < 0.001$ ). In contrast, the performance of the dysarthric patients did not vary according to the task: reading and number counting in syllables/exhalation ( $P = 0.821$ ) or words/exhalation ( $P = 0.785$ ).

**CONCLUSIONS:** The mean numbers of words and syllables per exhalation among dysarthric subjects did not vary according to the speech task used but they clearly showed differences between dysarthric patients and normal healthy subjects. The study also made it possible to obtain preliminary data on the average numbers of words and syllables per expiration produced by healthy individuals during their speech production.

## INTRODUCTION

Dysarthria refers to a group of speech disorders that arise from disruptions to the neuromotor control over muscle activities that are necessary for speech production. It occurs after damage to the central and/or peripheral nervous systems.<sup>1,2</sup> Dysarthria can affect the performance of the pulmonary, laryngeal and pharyngeal structures as well as the oral and nasal cavities. Together, these provide the basis for phono-articulatory functions: respiration, phonation, resonance, articulation and prosody.<sup>3</sup>

With regard to respiration, a distinction in this function is made in the literature, between silent or vital respiration and respiration for speech. For phonatory activity, the higher the volume of air required, the greater the number of muscles involved. For speech, breathing takes place through recruitment of respiratory muscles, the skeletal musculature (controlled by nerve impulses) and the central nervous system, which allows release of the air current. This air current needs to generate sufficient air pressure to vibrate the vocal folds. Besides a large air volume, speech needs a slower respiratory rate and extended expiratory phase.<sup>4</sup> Therefore, motor speech assessment of basal respiration in dysarthric patients often investigates vital capacity, respiration type and respiration rate (cycles per minute).<sup>3,5</sup>

Because all speech is produced upon exhalation, adequate respiratory support and coordination are essential for normal oral communication.<sup>6</sup> Patients with damage to sensory or motor components of the respiratory system may have difficulty in maintaining adequate respiratory support for speech, as well as in coordinating exhalation with phonation and articulation.<sup>7</sup> The breath group can serve as a functional unit for defining temporal features in continuous speech. These features of the breath group are determined by the physiological and linguistic demands of communication.<sup>8</sup>

There are speaking tasks that vary in these demands, such as number counting (from 1 to 20), reading and spontaneous speech,<sup>3,9</sup> and these are commonly used to evaluate speech performance for research and clinical applications. These tests provide a quantitative and qualitative analysis by yielding objective measurements and the number of items produced per exhalation, and also allow investigation of individual speech. This is important because analysis on pneumo-phono-articulatory coordination also encompasses aspects such as use of residual air in utterances, sentence intelligibility and use of pauses at expected times and positions within utterances during a conversation.<sup>6,10</sup> In fact, reduced mean length and variation of breath groups can cause inappropriate location of breath pauses that changes intonation and grammatical boundaries. Thus, these features reduce the intelligibility of speech and the communicative efficiency.<sup>11,12</sup>

Given the claims in the current literature that the locations and durations of breath groups are determined by physiological needs, linguistic accommodations and cognitive demands,<sup>10,11</sup> it is worth mentioning that these features can differ across speaking tasks and language spoken. In Brazil, no data on the number of words per exhalation is available. However, a normative value of 25 phrase elements per breath among Portuguese speakers has been proposed in a book, without specifying the speech task used.<sup>13</sup> Regarding individuals with speech disorders, a Brazilian study on 60 dysarthric patients found a mean of 7.7 words per breath for number counting and 6.8 words per breath in spontaneous speech, but there were no data for healthy speakers regarding these tasks.<sup>3</sup> Although words per breath is a valuable measurement, especially considering the linguistic approach, it is not meaningful for international comparisons. In this regard, measurements based on syllable units have been recommended.<sup>5</sup> Considering the importance of respiration in relation to speech and its implications for diagnosis and rehabilitation of dysarthric patients, studies are necessary in this field, taking into account the different tasks and the Portuguese language.

The aim of the present study was to analyze the number of words and syllables per exhalation among speakers with and without speech disorders, in two tasks assessing pneumo-phono-articulatory coordination (number counting and text reading), and to compare the performance of dysarthric speakers with the performance of non-dysarthric individuals in these two tests by analyzing the numbers of words and syllables per exhalation in these groups.

## METHODS

The present cross-sectional study was carried out in the Department of Speech, Language and Hearing Sciences at the Federal University of São Paulo (Universidade Federal de São Paulo). The study had previously been approved by this institution's research ethics committee (permit number 0069/11).

The sample comprised a patient group of 31 individuals with dysarthria who had previously been assessed at the Neuropsycholinguistics Laboratory and a control group of 31 healthy individuals who were matched for sex, age and education level. Body type was not controlled for in this study, since there is no consensus regarding whether body type influences speech breathing.<sup>14</sup> Moreover, a more recent study with a larger sample has suggested that there is no difference between speech tasks (counting and reading) and body type (endomorph, mesomorph or ectomorph).<sup>15</sup>

The dysarthric group consisted only of native speakers of Brazilian Portuguese with a single diagnosis of dysarthria acquired in adulthood and a medical diagnosis of neurological disorder. All the patients performed the tests to assess the number of words per exhalation in the number-counting and text-reading tasks of the dysarthria protocol.<sup>5,16,17</sup> Individuals with other speech, language and/or cognitive disorders that were investigated during the overall neuropsychological assessment were excluded from the study. The data relating to the dysarthric group were collected from patients who had previously been evaluated at the outpatient clinic for speech and language neurological disorders.

The control group included only Brazilian-Portuguese native speakers who were companions or family members of the patients assessed at the Neuropsycholinguistics Laboratory. The general exclusion criteria were as follows: history of alcoholism or drug use, history of communication disorders, current or previous neurological and/or psychiatric diseases, use of psychotropic medications and absence of visual or auditory impairments that might affect the outcome from the tasks. Data relating to the control group were prospectively collected in accordance with the matching proposed in the study design. All of these data were obtained by the same examiner under the same professional supervision.

Upon application of the tests, the subjects were first instructed, after one inspiration, to start counting from 1 to 20 aloud at their natural speech rate and to pause for breath as many times as necessary to finish counting. Then a text that had been written in a standard format and typed using the font Arial 14 was given to each subject. They were asked firstly to read it through to become familiar with the story and then to read it again, out aloud at their usual speed of reading. The text used for this evaluation comprised 129 words, which is the average number that has been suggested in many international protocols<sup>17,18</sup> (**Appendix 1**<sup>16</sup>).

The number of inhalations made during the two tasks was counted, from the first inhalation prior to the counting and reading tasks, to the last one made that was made just before the end of the tasks. The number of words and the number of syllables produced were then divided by the total number of inhalations.

Wilcoxon's nonparametric test (5% significance level) was applied to compare the performance of the dysarthric group

regarding the numbers of syllables and words in the two tasks. Matching and comparison of the two groups (healthy and dysarthric) in each speech task, regarding the numbers of syllables and words, was performed using the Mann-Whitney test at the 5% significance level.

## RESULTS

### Sample characteristics

The two groups were matched for sex, age and education level. The sample consisted predominantly of men (68%), such that each group comprised 21 men and 10 women. The variables of age and education (numbers of years of schooling with approval to pass to the next level), along with means and standard deviations, are shown in **Table 1**. Because the samples were matched, there was no statistically significant difference between the groups regarding age, sex and schooling years.

With regard to the etiology of the dysarthric patients, 16 (51.6%) had the non-progressive type of dysarthria: fourteen had suffered a stroke and two had had a traumatic brain injury. Fifteen (48.3%) presented progressive etiology: three had amyotrophic lateral sclerosis, one had Huntington's disease, five had Parkinson's disease, 5 had ataxia (different types) and one had dystonia. Regarding the frequency distribution of dysarthria types, the most prevalent was mixed (25.8%) followed by hypokinetic (22.6%), upper motor neuron (16.1%), flaccid (12.9%), spastic (12.9%), hyperkinetic (6.5%) and ataxic (3.2%).

The means and standard deviations for the numbers of words per exhalation (WPE) and syllables per exhalation (SPE) in the number counting and text reading tasks, together with the comparison between the two groups (values from the Mann-Whitney test), are shown in **Table 2**. Dysarthric patients performed worse than healthy controls.

In order to ascertain whether the two tasks were equally useful for identifying impairments in pneumo-phono-articulatory coordination, the performance of individuals with dysarthria was compared between the two tasks and between the two measurements (syllables and words). There was no statistically significant difference in the number of words or number of syllables per exhalation produced by the dysarthric group in the two tasks (**Table 3**).

## DISCUSSION

The main finding from this study was that the speech breathing tests (number-counting and reading), using words or syllables as the parameter, were sensitive for identifying alterations of respiration, which are one of the motor components of dysarthria. This study showed clear differences between dysarthric patients and normal healthy subjects. In addition, we were able to obtain data that can be used as clinical reference values for speech breathing assessment. Another relevant finding was that the

**Table 1.** Sample characteristics regarding the variables of sex, age and education level

	Classification		P-value
	Dysarthric	Healthy	
<b>Sex (n; %)</b>			
Female	10 (32.3%)	10 (32.3%)	1.000*
Male	21 (67.7%)	21 (67.7%)	1.000*
<b>Age (years)</b>			
Mean	50.9	50.3	0.877**
SD	17.7	17.5	
<b>Education level (years)</b>			
Mean	7.4	7.4	0.836**
SD	4.1	4.5	
N	31	31	

SD = standard deviation. \*Chi-square test; \*\*Mann-Whitney test; P ≤ 0.05.

**Table 2.** Comparison between numbers of words and syllables per exhalation produced by dysarthric patients and healthy individuals in number-counting and text-reading tasks

	Classification		Mann-Whitney test (P)	Result
	Dysarthric	Healthy		
<b>Number counting (WPE)</b>				
Mean	5.1	11.3	< 0.001*	Dysarthric < Healthy
SD	4.4	7.4		
N	31	31		
<b>Number counting (SPE)</b>				
Mean	10.7	23.2	0.001*	Dysarthric < Healthy
SD	9.3	15.3		
N	31	31		
<b>Text reading (WPE)</b>				
Mean	5.7	8.5	0.001*	Dysarthric < Healthy
SD	4.4	4		
N	31	31		
<b>Text reading (SPE)</b>				
Mean	11.9	17.8	0.001*	Dysarthric < Healthy
SD	9.1	8.4		
N	31	31		

WPB = words per breath; SD = standard deviation; SPE = syllables per exhalation. Mann-Whitney test (P ≤ 0.05).

**Table 3.** Comparison of number of words per exhalation (WPE) and of syllables per exhalation (SPE) produced on tasks in dysarthric group

	Counting	Reading	Wilcoxon's test (P)	Result
<b>WPE</b>				
Mean	5.1	5.7	0.785	counting = reading
Median	3.0	4.7		
Minimum	1.0	1.0		
Maximum	20.0	21.0		
Standard deviation	4.4	4.4		
n	31	31		
<b>SPE</b>				
Mean	10.7	11.9	0.821	counting = reading
Median	6.3	9.8		
Minimum	2.1	2.1		
Maximum	42.0	43.6		
Standard deviation	9.3	9.1		
n	31	31		

performance of the dysarthric group did not differ between the two tasks. These and other results are discussed further below.

Regarding sample characterization, the most frequently found etiology among the patients was cerebrovascular disease, and there were more males than females, thus corroborating the findings from previous studies.<sup>19,20</sup> Although there were more males in our sample, previous studies have observed no difference in speech breathing between the sexes.<sup>21</sup> Regarding schooling, the mean duration was found to be 7.4 years, equivalent to incomplete elementary school. Studies have shown that in Brazil, the users of the public healthcare system still predominantly have low literacy levels.<sup>22,23</sup>

Age also constitutes an important factor in brain lesions. The patients' mean age was 50.9 years (**Table 1**). Younger individuals are expected to be less vulnerable to risk factors that can cause neurological lesions, whereas older adults may present greater numbers of associated risk factors,<sup>22</sup> although there is no consensus in this regard in the literature.<sup>24,25</sup> Moreover, the age at the onset of degenerative conditions is highly variable.

The most prevalent form of dysarthria, occurring in 25.8% of the patients, was the mixed type. In this, individuals exhibit the combined characteristics of different forms of dysarthria and have lesions involving multiple areas of the central and/or peripheral nervous system, as occurs in degenerative diseases. It is important to point out that the most common etiology among our patients was non-progressive and the most frequent cause was stroke.

The number of words per exhalation in the two tasks among the dysarthric individuals was lower than values previously reported in the Brazilian literature, which were 7.7 words per exhalation in the counting task and 6.8 in the text-reading task (**Table 2**). As mentioned previously, no data for these tests are available.<sup>3</sup> The findings from this previous study cannot easily be compared with those of the present study, because there are different types and degrees of motor speech disorders that compromise respiration, phonation, articulation, resonance and prosody in many ways in dysarthric patients. For sensory-motor evaluation of speech, it is important to understand how each deficit in any motor component can impact speech production, and intra and interarticulatory factors need to be extensively examined.

The values from individuals without speech disorders, shown in **Table 2**, are helpful for establishing the magnitude of the deficit (in comparison with patients) and for following up the rehabilitation process.<sup>26</sup> Rehabilitation of speech encompasses all motor bases, including respiration, which underpins the other ones. The primary function of breathing is gas exchange (quiet respiration), but breathing also generates airflow and pressure to produce the voice and speech.

Breathing for the speech function is a refinement of vital respiration, in which individuals use around 20% of the total volume of the lungs, compared with around 10-15% for quiet respiration.

There is also a difference in respiratory rate, such that it is slower in speech, averaging eight cycles per minute, compared with 16-18 cycles in quiet respiration. Another important difference is exhalation during speech, which can be up to forty seconds long, while inhalation accounts for only 10% of the total respiratory cycle, whereas the ratio of the breathing phases for quiet respiration is 1:1.<sup>4</sup> There is a difference in breathing for these two functions.

As shown in **Table 2**, there was a difference in coordination between respiration and phonation, between the dysarthric and control groups. For speech production, greater intensity of neural motor refinement is required, such that coordination of breathing is fundamental for voice and speech production. Moreover, motor control for air inspiration and volume, depth of inspiration and control of expiration needs to be taken into consideration.<sup>6</sup> Determining how speech tasks affect breath group organization is important, because these tasks are often an integral part of the clinical assessment battery that is used to evaluate dysarthria.<sup>8,16</sup> In addition, understanding of breath group patterning is important for improvement of naturalness of speech. Furthermore, proper intonational variations within the breath group provide listeners with cues about linguistic and grammatical structures.<sup>8,11,12</sup>

No statistically significant difference in the numbers of words or syllables per exhalation was found among the dysarthric patients (**Table 3**). This was probably because the tasks and the measurements are probably equally sensitive for making the diagnosis, given that pneumo-phono-articulatory coordination is impaired in dysarthric patients.

There is a relationship between lung volume and duration of utterance, in which the magnitude of the lung volume is influenced by the length of the utterance to be produced. In reading, the grammatical structure of the utterance is a factor that influences pauses.<sup>27</sup> Thus, during text reading, syntactically determined inspirations occur, i.e. inspirations dictated by the text structure. Consequently, there is a relationship between the relative amount of air inspired and the location of the syntactic pauses, thus leading to some expected inspiration during reading.

Utterances are influenced not only by type and syntactic structure, but also by voice quality and intensity and the oral projection required. These factors can lead to different results from the tasks. However, the discourse of individuals with dysarthria contains more pauses between and within phrases, and may occur within words in more severe cases. Such pauses are incongruent and indicate pneumo-phono-articulatory incoordination among these speakers.<sup>7</sup>

Although the two tasks, reading and counting, differ and can assess different speech abilities, they are equally sensitive for measuring the number of words per exhalation, with regard to assessing basal breathing and pneumo-phono-articulatory coordination. This information may be especially useful in situations in which reading cannot be applied, such as in cases among patients

with visual deficits or who are illiterate or have low literacy levels. Thus, a task that makes use of automatism, and which can reliably assess pneumo-phono-articulatory coordination and is independent of educational level, is a useful alternative for speech breathing assessment.

The limitations of this study were, firstly, that it was a cross-sectional study. Thus, although the tasks could identify differences between dysarthric and normal subjects, the data obtained from normal subjects should not be understood as normative but only as preliminary. Secondly, patients with different types of dysarthria were evaluated. Further studies should be conducted in order to more precisely investigate the impact of respiration on speech production in situations of different types and degrees of dysarthria. In addition, more studies should investigate speech breathing among normal healthy subjects, taking different linguistic tasks into consideration.

## CONCLUSION

The mean numbers of words and syllables per exhalation among dysarthric individuals were the same in the two tasks used (automatism and text reading), but the values for the patients differed significantly from those of the healthy individuals. Both of these tasks are useful for speech breathing assessments among dysarthric patients.

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**Appendix 1.** Text used in reading task<sup>16</sup>

Um homem velho, que vivia sozinho há muito tempo, não suportava crianças. Ele morava numa casa grande e mantinha uma vara de bambu ao alcance de sua mão, com a qual ameaçava as crianças de um prédio BHN vizinho. Um dia, quando ele estava destruindo um ninho de pardais, ficou preso sobre o telhado alto de três metros e cinquenta. Isso porque, querendo descer muito rápido, deixou cair a escada que tinha colocado mal equilibrada contra a parede do sobrado. Como o homem começou logo a gritar, um garoto corajoso, que brincava calmamente na rua, levantou a cabeça, compreendeu a situação e recolocou a escada caída no chão ao lado de uma roseira. Depois dessa vergonhosa aventura, ele ofereceu ao menino um lanche acompanhado de suco de maçã.



# *Helicobacter pylori* infection in family members of patients with gastroduodenal symptoms. A cross-sectional analytical study

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## KEY WORDS:

*Helicobacter pylori*.

Disease transmission, infectious.

Family.

Parents.

Siblings.

## ABSTRACT

**BACKGROUND:** Primary *Helicobacter pylori* (*H. pylori*) infection is acquired predominantly in childhood in the family setting. We aimed to investigate the presence of intrafamilial concurrent *H. pylori* infection.

**DESIGN AND SETTING:** Cross-sectional analytical study with a control group, conducted in a tertiary care hospital.

**METHODS:** Fifty adult patients with gastroduodenal symptoms who underwent gastroscopy (index parents), their spouses and their children were enrolled in the study. Blood samples were collected from all of the study subjects to test for immunoglobulin G (IgG) antibody response. *H. pylori* antigen was investigated in the stool specimens of children only.

**RESULTS:** The participants were divided into two groups: Group 1 consisted of the 40 patients in whom *H. pylori* infection was demonstrated via endoscopy, their spouses and their children. Group 2 included the remaining 10 patients who underwent endoscopy revealing negative results for *H. pylori*, their spouses and their children. IgG antibodies were present in all of the index parents, 95% of their spouses and 93% of their children in group 1; 13 of the children (9%) were also positive for *H. pylori* stool antigen (HpSA). However, IgG antibodies were present in only 2 of the 10 index parents in group 2. One of their spouses and one of their children had a positive antibody response. All of their children had negative stool antigen test results.

**CONCLUSION:** *H. pylori* infections exhibit intrafamilial clustering. Parental infection, age  $\geq 7$  years and having three or more siblings are the major risk factors for *H. pylori* infection in children.

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is the causative agent of peptic ulcer disease and chronic gastritis. It also underlies gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer. The estimated prevalence is almost 70% in developing countries, and 30-40% in the United States and other industrialized countries.<sup>1</sup> In a recent study conducted in Turkey, the prevalence of *H. pylori* infection was reported to be 82.5% in the adult population.<sup>2</sup> In developing countries, it is markedly more prevalent at younger ages than it is in developed countries.<sup>3</sup>

Contact with *H. pylori* occurs usually during the first decade of life. *Helicobacter* seropositivity has been found to increase with age.<sup>4</sup> It has been reported that more than 30% of subjects acquired infection before the teenage period.<sup>5</sup> Ertem et al. investigated the age-related prevalence of *H. pylori* infection in a group of healthy children. They found that one in five of the children became infected before reaching four years of age and that one in two of the children aged under 11 years was infected.<sup>6</sup> Transmission is most likely to occur person-to-person, and through fecal-oral and oral-oral routes. Low socioeconomic status, poor environmental conditions and living in a crowded house have all been correlated with higher prevalence rates. Better hygiene practices and less household overcrowding have contributed to the decline in prevalence over the last decade.<sup>7</sup>

There are several invasive and noninvasive methods for diagnosing *H. pylori* infection.<sup>8,9</sup> Specific endoscopic findings, the rapid urease test (RUT), histological assessment and gastric tissue cultures all contribute towards making an accurate diagnosis. Molecular methods may be used to prove the presence of *H. pylori*. Noninvasive methods include the urea breath test (UBT), serological tests and stool antigen testing.<sup>10,11</sup> Detection of *H. pylori* antigen in stools provides evidence of active infection. This has been found to be highly concordant with the 13-carbon urea breath test (<sup>13</sup>C-UBT).<sup>12</sup> The stool antigen test is useful for primary diagnosis as well as for assessment of eradication following therapy.<sup>13</sup>

In this study, we determined the *H. pylori* status of family members, to reveal intrafamilial concurrent infection.

**METHODS**

**Study design, setting and ethics**

This was a cross-sectional analytical study, conducted in a tertiary care hospital in Istanbul in Turkey. The study was approved by the institution’s Internal Review Board (18/12/2012-174). The procedures followed were in accordance with the ethical standards of the Helsinki Declaration and its revisions. Informed consents were obtained for participation in the study.

**Patient population**

All adult consecutive patients with gastroduodenal symptoms who underwent gastroscopy were recruited for this study because this procedure provided a definitive diagnosis of *H. pylori* infection in the index case. These patients were enrolled in the study provided that their spouses and children also agreed to enter the study.

**Investigations for *H. pylori***

The presence of *H. pylori* was determined using RUT (CLOtest) and gastric histological evaluations on biopsy specimens collected by means of endoscopy. Blood samples were drawn from all patients, their spouses and children. Serum samples were stored at -20 °C and were assayed for anti-*Helicobacter* immunoglobulin G (IgG) antibodies (anti-Hp) using a micro enzyme-linked immunosorbent assay (ELISA) (Premier *H. pylori*, Meridian Diagnostics, Inc., Ohio, USA). The assays were performed in accordance with the manufacturer’s instructions. Stool samples were obtained only from the children and were frozen at -20 °C. *H. pylori* antigen was determined from the stool specimens using the Premier Platinum *H. pylori* stool antigen (HpSA) enzyme immunoassay (Meridian Diagnostics, Inc., Ohio, USA) as recommended by the manufacturer. Almost all of them were collected in the hospital. Only a few samples were obtained at home, and these were transferred in cold packs.

**Statistics**

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software (SPSS Inc., Chicago, IL, USA). The chi-square test and Fisher’s exact test were used.  $P < 0.05$  was considered statistically significant.

**RESULTS**

Fifty adult patients who underwent gastroscopy (index parents), their spouses (n = 50) and their children (n = 159) were enrolled in the study. Two groups were set up based on the infection status of the index parents: Group 1 consisted of the 40 patients with documented *H. pylori* infection (both RUT and histological evaluations revealing positive results), along with their spouses and children. Group 2 included the remaining 10 patients who underwent

endoscopy that did not confirm the presence of *H. pylori* infection, along with their spouses and children. The demographic characteristics of the sample are summarized in Table 1.

The index parents in group 1 were all seropositive. Anti-Hp IgG was found in 38 of their spouses (n = 40) and 130 of their children (n = 140). Stool antigens were detected in only 13 of these children, who were all seropositive. In contrast, anti-Hp was demonstrated in only two of the 10 index parents in group 2; one of their spouses (n = 10) and one of their children (n = 19) also had IgG antibodies. Stool testing for *H. pylori* antigen revealed negative results in all of the children in group 2 (Table 2).

**Table 1.** Demographic characteristics of the sample

	n	Age (years)		Gender n (%)	
		Mean ± SD	Age range	Female	Male
<b>Group 1*</b>					
Parents	80	36.4 ± 0.6	25-51	40 (50)	40 (50)
Children	140	7.7 ± 0.2	1.5-14	73 (52.1)	67 (47.9)
<b>Group 2**</b>					
Parents	20	34.8 ± 0.9	29-44	10 (50)	10 (50)
Children	19	4.4 ± 0.3	2-6	8 (42.1)	11 (57.9)
<b>Infected parents</b>	81	36.4 ± 0.6	25-51	41 (50.6)	40 (49.4)
<b>Non-infected parents</b>	19	34.8 ± 0.9	29-44	9 (47.4)	10 (52.6)
<b>Infected children</b>	131	7.9 ± 0.3	2-14	71 (54.2)	60 (45.8)
<b>Non-infected children</b>	28	4.5 ± 0.2	2-6	10 (35.7)	18 (64.3)
<b>Total study population</b>					
Parents	100	36 ± 0.5	25-51	50 (50)	50 (50)
Children	159	7.3 ± 0.2	1.5-14	81 (50.9)	78 (49.1)

SD = standard deviation. \*Group 1 included the 40 index parents with documented *H. pylori* infection, their spouses and their children; \*\*Group 2 consisted of the 10 index parents who underwent endoscopy revealing negative results for *H. pylori*, their spouses and their children.

**Table 2.** Presence of *H. pylori* (Hp) immunoglobulin G (IgG) antibodies and stool antigen in the family members in relation to the *H. pylori* status of the index parent who underwent endoscopy for gastroduodenal symptoms

	Group 1		Group 2		p
	n	%	n	%	
<b>Anti-Hp, index parent (n = 50)</b>					
+	40	80	2	4	< 0.01
-	0	0	8	16	
<b>Anti-Hp, spouses (n = 50)</b>					
+	38	76	1	2	< 0.01
-	2	4	9	18	
<b>Anti-Hp, children (n = 159)</b>					
+	130	82	1	1	< 0.01
-	10	6	18	11	
<b>HpSA, children (n = 159)</b>					
+	13	8	0	0	> 0.05
-	127	80	19	12	

HpSA = *H. pylori* stool antigen.

The children were evaluated for the risk factors of *H. pylori* infection. The risk of *H. pylori* infection was higher if both parents were infected and with increasing age among the children and greater numbers of siblings (Table 3). Children with positive test results (serological tests and/or positive stool antigen test) were asked about any symptoms of *H. pylori* infection (abdominal pain, dyspeptic signs and gastrointestinal bleeding). All of them were symptom-free.

## DISCUSSION

Transmission of *H. pylori* from infected family contacts has become a subject of research through observations of infection in more than one family member.<sup>14-15</sup> These studies have differed regarding their study designs (longitudinal or cross-sectional) and study populations (community-based or focusing on the families of *H. pylori*-positive patients). Most of the studies have been carried out either on families randomly selected from the general population or on the family members of children in certain age groups. On the other hand, some studies have approached this topic from the starting point of *H. pylori*-positive patients or patients with gastroduodenal symptoms and have then investigated their families. The present study was conducted among patients who had been referred to an adult gastroenterology clinic, and we subsequently assessed the infection status of their family members.

Various diagnostic tests have been used in research exploring the intrafamilial transmission of *H. pylori*. These tests have comprised anti-Hp, UBT, HpSA and RUT, along with molecular methods such as the polymerase chain reaction (PCR).<sup>16-24</sup> In our study, the infection status of the index parents was definitively determined by means of RUT and histological evaluations. The spouses and children were tested via serological tests, while a stool antigen kit was also provided for the children.

The most important finding from this study was the high seropositivity observed among the children (82.4%). The previously reported local seropositivity rates were 33%, 49.5% and 43.9% respectively.<sup>5,6,14</sup> The considerably high level of seropositivity found here can be attributed to the fact that 93.9% of those children had both parents infected with *H. pylori* who had been suffering gastroduodenal symptoms. This increases the chance of transmission. Lower rates might have been observed in community-based studies.

The key role of parents in transmitting *H. pylori* to their children has been shown in various population-based studies.<sup>14-21</sup> Dominici et al. assessed the infection rate of children in relation to their parents' infection status, using IgG antibodies. They reported that children whose parents were both seropositive had double the risk of being infected, compared with those whose parents were both seronegative.<sup>15</sup> In another study, the infection status was

determined using UBT among children and salivary IgG antibodies among their parents. It was concluded that infected parents, especially mothers, played a key role in the transmission of *H. pylori* to their children.<sup>16</sup>

Weyermann et al. conducted a prospective birth cohort study to investigate the acquisition of *H. pylori* infection in early childhood and to clarify the role of parental infection status in the transmission of *H. pylori* to children. Mothers who gave birth to a healthy child, their partners and their other children were included in the study. The presence of active infection of the mothers with *H. pylori* was determined using UBT. The infection statuses of the fathers at the beginning and of their children at the ages of one, two and three years were determined by means of HpSA. These authors claimed that an infected mother was likely to be the main source for *H. pylori* infection among their children. Kissing, shared use of spoons, cleaning pacifiers (dummies) or teats of feeding bottles in the mouth and sharing a bed may facilitate its spread.<sup>17</sup>

Evidence of mother-child transmission of infection was also reported in an article by Escobar and Kawakami.<sup>18</sup> Nahar et al. screened 55 families for *H. pylori* using a stool antigen test. Those who tested positive were further evaluated through culturing biopsy material or gastric juice. These authors then performed PCR-based random amplified polymorphic deoxyribonucleic acid (DNA) (RAPD) fingerprinting to explore the genetic diversity of *H. pylori* within families. They observed shared genotypes in the paired strains from mothers and children and concluded that vertical transmission was the most probable route of transmission.<sup>19</sup>

**Table 3.** Risk factors for *H. pylori* (Hp) infection in children. *H. pylori* infection was determined through a positive test result for either anti-Hp or *H. pylori* stool antigen (HpSA)

	Children with <i>H. pylori</i> infection (n = 131)	Children without <i>H. pylori</i> infection (n = 28)	OR	95% CI
<b>Infection status of the parents</b>				
Both parents infected	123	3	128.1	31.8-516.9
Only one or no parents infected	8	25		
<b>Age of children (years)</b>				
Age ≥ 7	83	12	2.3	1.0- 5.3
Age < 7	48	16		
<b>Sex of children</b>				
Girl	61	14	0.9	0.4-2.0
Boy	70	14		
<b>Number of siblings</b>				
≥ 3	106	1	114.5	14.8-883.0
< 3	25	27		

OR = odds ratio; CI = confidence interval.

Early diagnosis and prompt treatment of patients might prevent the spread of infection to spouses and children. In the present study, we observed that parental infection was a risk factor for children. However, the mothers' role in the transmission could not be documented, since the proportions of infected mothers and fathers among the infected parents were not significantly different and both spouses were infected in most cases.

Several studies on intrafamilial transmission have been conducted among the parents and siblings of children who either had been referred due to gastroduodenal symptoms or had previously been found to present *H. pylori*-positive status. Drum et al. demonstrated that parents of *H. pylori*-positive children were more likely to have a positive serological response than were the comparably-aged parents of noncolonized children, thus indicating the existence of intrafamilial clustering of *H. pylori* infection.<sup>22</sup> In another study, *H. pylori* infection was investigated by means of upper gastrointestinal endoscopy and UBT in 100 children with upper gastrointestinal symptoms. UBT was performed on all family members of each index patient. The prevalence of *H. pylori* infection was significantly higher among the families of infected children.<sup>23</sup> After analyzing 35 children with *H. pylori* gastritis and their family members, Yokota et al. concluded that intrafamilial infection was the dominant transmission route.<sup>24</sup>

All of the above studies focused on index pediatric patients. Our study differed from these through focusing on parents with gastroduodenal symptoms and concentrating on the infection status of their family members. We demonstrated that among the 126 children whose parents were both infected, 123 had a positive test result for either anti-Hp or HpSA. On the other hand, when the parents were not infected, their children were not infected either (Table 3). This reflects exact clustering of the infection in the family, thus suggesting that close personal contact facilitated transmission. These families belonged to a middle-class socioeconomic group, and there seemed to be no other risk factor attributable to their living conditions. All of their homes had a water supply from the city and were connected to the sewer system.

There have been reports mentioning higher prevalence of infection among spouses.<sup>25-28</sup> Brenner et al. assessed the clustering of *H. pylori* infection among healthy couples. Active infection was measured by means of the urea breath test and HpSA. Their results supported the hypothesis that spouse-to-spouse transmission had a major role in *H. pylori* infection.<sup>29</sup> However, several years after that report, the same researchers assessed clustering of *H. pylori* infections in both high and low-prevalence population subgroups. They stated that spouse-to-spouse transmission of infection was unlikely to be of relevance in low-prevalence population groups, although clustering of infection was observed in high-prevalence population groups.<sup>30</sup>

Horizontal transmission of *H. pylori* may play an important role in developing countries. However, improved sanitation and quality of life have markedly reduced the risk in developed countries, which has thus enhanced the role of intimate contact in intrafamilial infection. In the present study, we observed seropositivity in 38 spouses of the 40 *H. pylori*-positive index patients (95%). On the other hand, only one out of the 10 *H. pylori*-negative index patients had a seropositive spouse.

Children play a role in spreading *H. pylori*. Infection may be transmitted among siblings. We documented that sibship size was a risk factor (Table 3). 99% of the children were infected when the number of siblings was  $\geq 3$ , whereas 48% were infected when the number of siblings was  $< 3$ . The role of siblings in the transmission of infection has previously been reported.<sup>23,31-33</sup> Infection among siblings may be of more relevance in high-prevalence countries. Transmission probably occurs in early childhood, from older to younger siblings.<sup>31,32</sup>

The prevalence of infection among the children was quite high, with an overall seropositivity rate of 82%. However, only 13 children who were seropositive were also positive for HpSA. This ratio (8%) was unexpectedly low. The HpSA test has been found to be a reliable method for diagnosing and following up *H. pylori* infection. It is considered useful for screening and monitoring.<sup>34</sup> In order to perform diagnostic tests other than serological tests, waiting two weeks after the end of proton pump inhibitor therapy and four weeks after the end of antibiotic therapy is recommended.<sup>3,34</sup> Prior antibiotic therapy or spontaneous elimination of *H. pylori* infection<sup>35</sup> may explain the high seropositivity rate (82% of the children in the present study) alongside the low positivity rate for stool antigen (8%) in those children. Constipation, presumably due to degradation of *H. pylori* antigens, may also contribute to this result.

*H. pylori*-positive patients pose a risk of transmission of infection to their other family members. We observed that if one of the parents was infected with *H. pylori*, the risk of infection was significantly higher for their spouses and children. When both parents were infected, their children had a higher rate of infection than did children with only one or no parents infected. Crowded living conditions (number of siblings  $> 3$ ) increased the risk. These findings support the notion that transmission occurs from person to person, through close contact, and that it occurs during childhood.

One limitation of the present study is that we did not prove that a single *H. pylori* strain caused the intrafamilial clustering in each family. Nonetheless, presence of a single strain would not constitute sufficient evidence of person-to-person transmission. The shared strain indicates only a common source, which may be an environmental factor as well. However, our patients had access to a water supply from the city and adequate sanitation facilities.

The joint European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/North American Society

for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines do not recommend starting treatment based on screening for the presence of *H. pylori* infection by means of a noninvasive test applied to children (recommendation 2c). Instead, they recommend testing for *H. pylori* among children with gastric or duodenal peptic ulcer disease (recommendation 3).<sup>34</sup>

Presence of *H. pylori* is a risk factor for duodenal ulcers in children.<sup>36</sup> Considering the fact that it is highly transmitted within family settings, presence of parental *H. pylori* infection should prompt physicians to ask children about any gastroduodenal symptoms compatible with peptic ulcer disease. Children with positive symptoms should be further evaluated for peptic ulcer disease.

There is a need to determine which symptoms should be interpreted as indicative of the presence of peptic ulcer disease. Hernandez et al. performed upper gastrointestinal endoscopy due to suspicion of peptic disease when at least one of the following manifestations was observed: hematemesis; chronic epigastric pain or nocturnal awakening with abdominal pain; chronic vomiting associated with eating; suspected peptic ulcer disease relapse; and recurrent abdominal pain in children with a first-degree relative with peptic ulcer disease. *H. pylori* infection was confirmed in 56.1% of the children and duodenal ulcer was diagnosed in 32 patients (13.5%).<sup>37</sup> Guariso et al. declared that upper gastrointestinal endoscopy was appropriate for cases with a family history of peptic ulcer and/or *H. pylori* infection, in individuals older than 10 years of age, with dyspeptic symptoms persisting for more than six months that were severe enough to affect activities of daily living.<sup>38</sup> Thus, analysis on the cost-effectiveness of further investigation of the patients with gastroduodenal symptoms compatible with peptic ulcer disease and a family history of *H. pylori* infection could form the subject of a further study.

## CONCLUSION

We observed concurrent intrafamilial *H. pylori* infection. It may have been transmitted within the family. Parental infection, age  $\geq 7$  years and having three or more siblings are the major risk factors for *H. pylori* infection in children. Infection of parents puts children at risk. The risk increases with age and number of siblings.

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# Body mass index and association with use of and distance from places for physical activity and active leisure among schoolchildren in Brazil. Cross-sectional study

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## KEY WORDS:

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## ABSTRACT

**BACKGROUND:** We evaluated associations between use of public places for physical activity and active leisure (PAAL) and their distances from subjects' homes and indicators of overweight and obesity, among schoolchildren from different socioeconomic levels, in the city of Florianópolis, Brazil.

**DESIGN AND SETTING:** Cross-sectional study conducted on a sample of 2,152 schoolchildren aged 7 to 14 years, enrolled at 30 public and private schools.

**METHODS:** The exposure variables were the use of public places for PAAL in the neighborhood and their distance from schoolchildren's homes. The outcomes were body mass index (BMI) and waist circumference (WC). Univariate and multivariate linear regression analyses were conducted according to income strata.

**RESULTS:** Among the schoolchildren from low-income families, living closer to parks/playgrounds was associated with lower BMI ( $\beta = -2.15$ ; 95% confidence interval, CI = -2.53; -1.77) and lower WC ( $\beta = -0.11$ ; 95% CI = -0.17; -0.05), while living at these distances from football pitches was associated with higher BMI ( $\beta = 1.73$ ; 95% CI = 0.31; 3.15) and larger WC measurements ( $\beta = 0.03$ ; 95% CI = 0.005; 0.14). Among the schoolchildren in low-income groups, living at an intermediate distance from beaches was associated with lower BMI ( $\beta = -1.10$ ; 95% CI = -1.61; -0.59).

**CONCLUSION:** Living closer to parks/playgrounds was associated with lower BMI and WC among schoolchildren from low-income families. Living closer to football pitches was associated with higher BMI and WC among these schoolchildren. Living at intermediate distances from beaches was associated with lower BMI among these schoolchildren.

## INTRODUCTION

There is evidence showing increasing prevalence of overweight and obesity among children and adolescents in high, medium and low-income countries.<sup>1</sup> Similar trends were observed in Florianópolis, capital of the Brazilian state of Santa Catarina, during the period from 2002 to 2007, among 7 to 10-year-old children,<sup>2</sup> and from 2007 to 2012, among 7 to 14-year-old children and adolescents.<sup>3</sup> In addition, in 2007 and 2008, the prevalence of abdominal obesity among 6 to 10-year-old schoolchildren in the state of Santa Catarina was observed to be 4.9%.<sup>4</sup>

Studies have shown that the availability of places for physical activity and active leisure (PAAL) close to home makes it more likely that these facilities will be used more often, because of ease of access.<sup>5</sup> Children and adolescents who report living close to such places tend to have lower body mass index (BMI) and lower values for other measurements of obesity.<sup>6,7</sup> It has also been indicated in the literature that there are differences in the patterns of usage of neighborhood facilities when different socioeconomic strata are investigated, whether assessed at the family<sup>8</sup> or area level (the latter based on area of residence).<sup>9</sup>

However, the majority of published studies evaluating individuals of school age have been conducted in high-income countries, located in the northern hemisphere. Consequently, there is a lack of clear evidence regarding associations between measurements of overweight and obesity among children and adolescents living in middle-income and medium-to-high income countries and access to facilities for PAAL in the environs of their homes.<sup>5,10,11</sup> Another gap in the literature is that the studies have assessed the environmental availability of public spaces in general, without analyzing different types of facilities separately or their relationships with adiposity-related outcomes.<sup>6,12-14</sup>

Florianópolis is the capital of the Brazilian state of Santa Catarina, which is located in the country's southern administrative region. In 2016, the municipal district had a population density of 707.4 inhabitants/km<sup>2</sup>.<sup>15</sup> Although the city of Florianópolis has a very high human development index (HDI; 0.847),<sup>16</sup> it also has an elevated Gini index of 0.5474 (the closer this index is to 1, the greater the social inequalities between residents are),<sup>17</sup> which might reflect differences in access to places for PAAL between wealthy and underprivileged areas.

The objective of this study was therefore to investigate associations between use of public places for PAAL, and their distance from subjects' homes, and indicators of overweight and obesity among 7 to 14-year-old schoolchildren from different socioeconomic levels, in the city of Florianópolis, Brazil.

## METHODS

### Ethics

This study was approved by the Human Research Ethics Committee at the Universidade Federal de Santa Catarina, under review process no. 120,341/2012. The guardians of all schoolchildren selected for the study were sent free and informed consent forms that they needed to sign before the children could be included in the study.

### Study design and participants

This was a cross-sectional study based on a probabilistic sample of 2,506 schoolchildren aged 7-14 years who were enrolled at public or private schools in Florianópolis. The sample was selected by means of clusters, according to: the municipal district's administrative regions; the type of school; the age group; and the number of students enrolled in each school. This procedure aimed to ensure that the sample was representative both of the regions in which the population lives and of the variability of income in the population. The sampling methods have been described in greater detail elsewhere.<sup>18,19</sup>

Based on the prevalence rates of the exposure variables and of each outcome, and considering a study power of 80%, a 95% confidence level, a 10% sample size margin to allow for confounding factors and a design effect of 1.8, this study had sufficient power to: a) detect that prevalence ratios of 0.82 to 0.85 would be protective factors and 1.18 to 1.23 would be risk factors for overweight/obesity; and b) detect that prevalence ratios of 0.50 to 0.60 would be protective factors and 1.68 to 2.01 would be risk factors for abdominal obesity.

### Data collection

#### Study exposure variables

The schoolchildren were given self-report questionnaires, created for this study, which they and/or their parents/guardians

answered. The questions included items asking about the frequency of use of, and perceived distance from home to places for physical activity and active leisure. These were chosen based on findings reported in the scientific literature that discusses these different types of places.<sup>20-25</sup> Four types of places for PAAL were investigated regarding their frequency of use and perceived distance from home, as follows: beaches, parks/playgrounds, sports courts and football (soccer) pitches. These data were coded as categorical polytomous variables (used weekly, used fortnightly, used monthly, used rarely and never used).

In a nationwide study conducted in Brazil, on 74,589 adolescents aged 12 to 17 years, the subjects who were considered physically active were those for whom the duration of leisure-time physical activity was  $\geq 300$  minutes per week.<sup>26</sup> In this light, and taking into account the possibility that each student might use several places in the vicinity of their homes, the variables of the present study regarding use of places were then re-categorized into two groups: did use them (covering weekly and fortnightly) and did not use them (combining used rarely, used monthly and never used).

The perceived distance from the family home to each type of place was surveyed in terms of the time taken to walk the distance in minutes. The responses were categorized as up to 10 minutes, from 11 to 19 minutes and 20 minutes or more, on the assumption that places that took up to 10 minutes to reach on foot were close to the home (approximately 800 meters) and could therefore be accessed actively, without the need for motorized transportation.<sup>27</sup>

The questionnaire answered by the children and their parents also contained questions on monthly family income and mothers' and fathers' educational levels. The parents' educational levels were classified into three categories (incomplete high school, complete high school, complete higher education). The schoolchildren's ages were analyzed both as a continuous variable and dichotomously in two categories according to the sampling frame applied (7 to 10 or 11 to 14 years of age), and the variable of type of school was divided into two categories (public or private). Monthly family incomes reported in Brazilian reais (R\$) were collected as a continuous variable and were then used to stratify the sample in terciles (high, medium or low-income families), in order to observe whether physical activity environments were associated with the outcome measurements differently for distinct socioeconomic strata. The terciles of monthly income that were used to separate the sample into low, medium and high-income strata were R\$ < 1,577 (first tercile), R\$ 1,577 to 3,001 (second tercile) and R\$ > 3,001 (third tercile).

#### Study outcome variables

Weight and height data were collected objectively by researchers who had been duly trained in accordance with the technical standards recommended by the World Health Organization

(WHO).<sup>28</sup> The absolute intra-examiner technical error of measurement (TEM) that was considered acceptable was twice that of the gold-standard anthropometrist, while the absolute inter-examiner TEM that was considered acceptable was three times the experienced anthropometrist's TEM.<sup>29</sup>

BMI, as evaluated according to the WHO criteria,<sup>30</sup> has shown high sensitivity (92.5%) for detecting excess body fatness in schoolchildren aged 7-10 years living in Florianópolis.<sup>31</sup> Hence, we defined overweight as BMI for age and sex  $\geq +1$  and  $< +2$  z-scores and obesity as BMI for age and sex  $\geq +2$  z-scores.<sup>30</sup> In addition, we evaluated waist circumference (WC) in our sample. This measurement was taken at least twice for each schoolchild. These data were used as continuous variables, in cm, in the analyses on associations. WC values were categorized using the criterion for abdominal obesity proposed by Fernandez et al.<sup>32</sup> (percentile  $\geq 90$  for age and sex as the cutoff point) to observe its prevalence in the sample.

### Statistical analyses

Data on the variables of use of places for PAAL and perceived distance from these places were taken to be the primary exposures. Their associations with the two continuous outcome variables BMI (in kilograms divided by meters squared) and WC (in centimeters) were tested using univariate and multivariate linear regression, with estimation of  $\beta$  coefficients and 95% confidence intervals (95% CI).

Exposure variables with P-values  $\leq 0.20$  for univariate associations with outcomes were entered into a multivariate model with forward selection in the order of their strength of association (the higher the P-value was, the earlier the variable was included in the multivariate model). Interactions between the environmental factors and the outcome were tested for sex and age strata first, prior to income stratification, and no differences relating to sex or age strata were observed in these correlations (data not shown).

A 5% significance level was used for hypothesis testing, considering type I error, and null hypotheses were rejected when the p-value was less than the type I error value. The *svy* command available in the Stata 13.0 software was used to account for the sample weights of each individual. When multivariate models had been constructed, their goodness of fit was analyzed using the Bartlett test (homogeneity of variance) for qualitative variables. Models were defined as presenting a good fit when they had P-values  $> 0.05$ .

### RESULTS

The study investigated 2,506 schoolchildren. Valid BMI data were obtained from 2,484, and there was at least one valid WC measurement for 2,480. Valid family income data were obtained in relation to 2,152 (85.9% of the sample).

**Table 1** lists the characteristics of the whole sample and those of the sample broken down according to family income strata. Overall, the prevalence of overweight was 21.5% and the prevalence

of obesity was 12.7%, thus showing that more than one third of the schoolchildren had excess body weight. Abdominal obesity was detected in 5.0% of those assessed. There were no significant differences in the mean body mass index or mean waist circumference between the income strata. In relation to the parents' educational level, it was observed that among the schoolchildren from the high-income stratum, more of both the mothers and the fathers had completed undergraduate university education (**Table 1**).

The data on the use of each of the different types of public places for PAAL showed that sports courts were the most popular, followed by beaches, parks/playgrounds and, finally, football pitches. Differences in the use of these places according to income strata were observed only in relation to parks/playgrounds, which were used more frequently by schoolchildren in the high-income group. Schoolchildren from the highest income stratum were the ones who most frequently lived closer to football pitches (**Table 1**).

The frequencies of use of all places for PAAL were significantly and progressively higher when places were near home (**Table 2**). Multivariate analyses showed that schoolchildren in the low-income group who live at intermediate and closer distances from parks/playgrounds had lower BMI values ( $\beta = -1.96$ ; 95% CI =  $-3.45$ ;  $-0.47$ ; and  $\beta = -2.15$ ; 95% CI =  $-2.53$ ;  $-1.77$ , respectively), compared with schoolchildren living far from these facilities. Schoolchildren from the low-income stratum who lived at an intermediate distance from beaches also presented lower values of BMI ( $\beta = -1.10$ ; 95% CI =  $-1.61$ ;  $-0.59$ ). These associations were also observed between higher values of BMI and intermediate and closer distances from football pitches ( $\beta = 1.67$ ; 95% CI =  $0.72$ ;  $2.62$ ; and  $\beta = 1.73$ ; 95% CI =  $0.31$ ;  $3.15$ , respectively) (**Table 3**).

**Table 4** shows that the same association that was observed between distance from home to parks/playgrounds and BMI was once again present in relation to the WC of schoolchildren in the low-income group ( $\beta = -0.11$ ; 95% CI =  $-0.17$ ;  $-0.05$ ). For schoolchildren living 11-19 minutes away from football pitches, an association with WC was also observed ( $\beta = 0.03$ ; 95% CI =  $0.005$ ;  $0.14$ ).

### DISCUSSION

This study analyzed the use of public places for PAAL and their distances from homes, and their associations with indicators of overweight/obesity among 7 to 14-year-old schoolchildren living in Florianópolis. The main findings were that associations existed in the stratum of schoolchildren in the low-income group between lower distances from parks/playgrounds and lower BMI and WC values; between lower distances from football pitches and higher BMI and WC values; and between living at an intermediate distance from beaches and lower values of BMI.

With regard to associations between indicators of overweight/obesity and socioeconomic characteristics, Boing and Subramanian<sup>33</sup> assessed a population of a different age in Florianópolis. Their study

enrolled 1,720 adults in 2009 and 2010, and it was observed that the BMI of women living in environments where educational levels were lower was 1.12 kg/m<sup>2</sup> higher than the same index among female

residents of areas with high educational levels ( $P < 0.05$ ). Since the schoolchildren of our sample who were from low-income families had less-educated parents (**Table 1**), it is reasonable to assume that

**Table 1.** Descriptive characteristics of the sample of 7 to 14-year-old schoolchildren, stratified according to monthly family income, Florianópolis, Santa Catarina, Brazil, 2012-2013

Variables	Categories	Total (n = 2,506)		Low income (n = 718)		Medium income (n = 736)		High income (n = 698)		P-value <sup>b</sup>
		n	%	n	% <sup>a</sup>	n	% <sup>a</sup>	n	% <sup>a</sup>	
Sex	Female	1,334	56.5	402	58.0	370	54.0	362	56.7	0.640
	Male	1,172	43.5	316	42.0	366	46.0	336	43.3	
Age (years)	7 to 10	1,530	61.1	436	61.2	473	63.9	415	63.0	0.589
	11 to 14	976	38.9	282	38.8	263	36.1	283	37.0	
Type of school	Public	1,637	65.3	672	93.9	585	80.7	201	26.2	<b>&lt; 0.001</b>
	Private	869	34.7	46	6.1	151	19.3	497	73.8	
BMI (n = 2,484)	(Mean; SD)	18.60	3.55	18.72	3.80	18.74	3.71	18.44	3.24	0.616
	Overweight <sup>†</sup>	511	21.5	469	65.6	473	65.6	467	65.7	0.995
	Obese <sup>†</sup>	315	12.7	241	34.4	256	34.4	226	34.3	
Waist circumference (n = 2,480)	(Mean; SD)	61.92	8.53	61.95	3.89	61.76	3.99	62.10	3.99	0.718
Abdominal obesity (n = 2,480)	Yes <sup>‡</sup>	134	5.0	51	6.6	48	5.5	25	3.7	0.198
Mother's educational level (n = 2,389)	Incomplete high school	851	33.3	443	63.5	272	35.3	65	7.6	<b>&lt; 0.001</b>
	Complete high school	857	37.5	210	32.5	336	49.1	210	32.7	
	Complete higher education	681	29.2	32	4.0	115	15.6	416	59.7	
Father's educational level (n = 2,086)	Incomplete high school	806	35.6	364	62.6	295	44.1	83	11.4	<b>0.002</b>
	Complete high school	710	35.3	144	31.0	268	44.7	215	30.0	
	Complete higher education	570	29.1	39	6.4	80	11.2	343	58.6	
Uses beaches (n = 2,382)	Yes	745	32.9	199	30.2	200	26.5	223	35.7	0.456
	No	1,637	67.1	489	69.8	522	73.5	462	64.3	
Uses parks/ playgrounds (n = 2,342)	Yes	642	27.5	169	23.2	183	24.1	205	32.6	<b>0.045</b>
	No	1,700	72.5	501	76.8	523	75.9	476	67.4	
Uses sports courts (n = 2,336)	Yes	1,100	45.3	325	47.4	322	41.3	309	45.0	0.288
	No	1,236	54.7	345	52.6	388	58.7	366	55.0	
Uses football pitches (n = 2,341)	Yes	661	25.4	209	26.1	214	25.2	159	23.5	0.836
	No	1,680	74.6	461	73.9	501	74.8	517	76.5	
Distance to parks/ playgrounds (minutes) (n = 1,830)	1-10	776	42.4	173	31.0	221	43.7	268	56.0	0.101
	11-19	419	22.9	150	30.3	126	19.5	103	14.3	
	≥ 20	635	34.7	178	38.7	202	36.8	179	29.6	
Distance to sports courts (minutes) (n = 1,508)	1-10	698	46.3	173	39.7	207	44.4	224	53.3	0.132
	11-19	372	24.6	127	30.0	114	20.7	92	22.2	
	≥ 20	438	29.1	117	30.3	157	34.9	111	24.5	
Distance to football pitches (minutes) (n = 1,244)	1-10	538	43.3	141	35.6	172	38.3	161	49.5	<b>0.002</b>
	11-19	306	24.6	101	29.7	106	31.3	71	21.1	
	≥ 20	400	32.1	123	34.7	128	30.4	97	29.4	
Distance to beaches (minutes) (n = 2,072)	1-10	476	23.0	122	20.4	138	21.7	144	20.9	0.829
	11-19	360	17.3	109	21.3	111	20.0	108	17.8	
	≥ 20	1,236	59.7	359	58.3	368	58.3	368	61.3	

BMI = body mass index; <sup>\*</sup>overweight 95% CI = 16.7-27.3%; <sup>†</sup>obese 95% CI = 11.0-14.5%; <sup>‡</sup>abdominal obesity 95% CI = 3.4-7.3%; <sup>a</sup>percentage values take into account the design effect (svy command); <sup>b</sup>P-value significant at 5% for Pearson's chi-square test.

**Table 2.** Frequency of schoolchildren using places for PAAL according to perceived distances from the places to home. Florianópolis, Santa Catarina, Brazil, 2012-2013

Frequency of use of places for PAAL	Perceived distance from home in time walking (minutes)						P-value*
	1 - 10		11 - 20		> 21		
	n	%	n	%	n	%	
<b>Uses beaches (n = 2,069)</b>							
Yes	300	67.2	150	42.6	277	23.2	< 0.000
No	174	32.8	210	57.4	958	76.8	
<b>Uses parks/ playgrounds (n = 1,826)</b>							
Yes	378	48.1	139	32.6	114	16.2	< 0.000
No	395	51.9	279	67.4	521	83.8	
<b>Uses sports courts (n = 1,505)</b>							
Yes	538	75.4	257	68.2	232	50.9	< 0.000
No	159	24.6	113	31.8	206	49.1	
<b>Uses football pitches (n = 1,237)</b>							
Yes	326	59.4	160	49.1	147	36.0	< 0.000
No	208	40.6	145	50.9	251	64.0	

\*Tendency from chi-square test.

**Table 3.** Crude and adjusted analyses on association between use of public places for physical activity and their distances from homes and body mass index, according to family income strata, among 7 to 14-year-old schoolchildren living in Florianópolis, Santa Catarina, Brazil, 2012-2013

Environmental variables	Low income				Medium income				High income			
	Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>		Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>		Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
<b>Uses beaches</b>												
No	0.00		-	-	0.00		0.00		0.00		0.00	
Yes	-0.01	-0.71; 0.69	-	-	0.25	-0.44; 0.95	0.21	-1.11; 1.53	<b>-0.33</b>	<b>-0.55; -0.09</b>	-0.10	-1.69; 1.49
<b>Uses parks/ playgrounds</b>												
No	0.00		0.00		0.00		0.00		0.00		-	-
Yes	-0.39	-1.12; 0.32	0.61	-0.79; 2.00	-0.45	-1.67; 0.77	-0.45	-2.01; 1.10	-0.56	-2.52; 1.40	-	-
<b>Uses sports courts</b>												
No	0.00		0.00		0.00		0.00		0.00		0.00	
Yes	0.58	-0.23; 1.40	0.79	-1.41; 2.99	0.008	-0.94; 0.96	-0.44	-2.32; 1.43	0.88	-0.58; 2.34	0.08	-3.23; 3.39
<b>Uses football pitches</b>												
No	0.00		-	-	0.00		0.00		0.00		-	-
Yes	0.59	-0.48; 1.67	-	-	-0.08	-1.39; 1.22	-0.15	-1.95; 1.65	1.12	-0.34; 2.57	-	-
<b>Distance to beaches (minutes)</b>												
1-10	1.08	-0.49; 2.67	0.94	-1.92; 3.80	-0.25	-0.59; 0.08	-0.65	-1.60; 0.31	0.13	-0.11; 0.38	-	-
11-19	-0.02	-1.31; 1.26	<b>-1.10</b>	<b>-1.61; -0.59</b>	-0.58	-2.05; 0.89	-0.81	-2.36; 0.75	-0.14	-1.50; 1.22	-	-
≥ 20	0.00		0.00		0.00		0.00		0.00		-	-
<b>Distance to parks/playgrounds (minutes)</b>												
1-10	-0.77	-1.92; 0.38	<b>-2.15</b>	<b>-2.53; -1.77</b>	-0.46	-1.65; 0.73	-	-	<b>0.78</b>	<b>0.44; 1.12</b>	1.11	-0.12; 2.34
11-19	-1.52	-3.29; 0.24	<b>-1.96</b>	<b>-3.45; -0.47</b>	0.10	-1.36; 1.56	-	-	0.86	-1.00; 2.72	0.07	-1.20; 1.35
≥ 20	0.00		0.00		0.00		-	-	0.00		0.00	
<b>Distance to sports courts (minutes)</b>												
1-10	0.93	-0.85; 2.71	-	-	0.06	-1.11; 1.23	0.41	-0.40; 1.23	0.10	-2.05; 2.27	-	-
11-19	0.34	-2.00; 2.69	-	-	0.02	-1.42; 1.46	0.13	-1.31; 1.55	-0.11	-3.43; 3.21	-	-
≥ 20	0.00		-	-	0.00		0.00		0.00		-	-
<b>Distance to football pitches (minutes)</b>												
1-10	<b>1.30</b>	<b>0.01; 2.59</b>	<b>1.73</b>	<b>0.31; 3.15</b>	-0.09	-1.53; 1.33	-	-	<b>0.81</b>	<b>0.38; 1.23</b>	-0.15	-0.68; 0.37
11-19	<b>0.53</b>	<b>0.18; 0.88</b>	<b>1.67</b>	<b>0.72; 2.62</b>	0.19	-0.98; 1.35	-	-	0.67	-1.02; 2.37	-0.01	-1.35; 1.32
≥ 20	0.00		0.00		0.00		-	-	0.00		0.00	

\*Multivariate models were controlled for the continuous variable of schoolchildren's age; <sup>a</sup>P-value significant at 5%; <sup>b</sup>Variables of use of and distance from football pitches presented collinearity.

these schoolchildren from low-income families also lived in areas where incomes and educational levels were lower, thus raising the hypothesis that other variables relating to inequalities in the economic environment (such as availability of safe places for physical activity and existence of pedestrian-friendly environments in residential areas<sup>9,34</sup>) may be mediating overweight/obesity. Similar results have also been observed in other countries, albeit high-income countries. Lakes and Burkart<sup>35</sup> assessed 28,159 children aged 5 to 6 years who were living in Berlin and observed that an increase of one point (on a scale from 4 to 8) in a family's social index (relating to socioeconomic level) resulted in a 68.5% reduction in overweight.

Concerning the proximity of homes to parks/playgrounds and the association of this factor with both outcomes in the low-income family stratum, Hsieh et al.<sup>36</sup> assessed Hispanic girls in Los Angeles, United States, who would be expected to have lower incomes than non-Hispanic residents. They found that the level of body fat was 1.4% lower among those who lived in neighborhoods with more

than three acres of space reserved for parks. The higher density of parks around adolescents' schools in Taiwan was also associated with lower values for waist circumference among boys.<sup>37</sup>

In relation to the association between intermediate distance from beaches to homes and lower BMI, Abbot et al.<sup>38</sup> found similar results among 1,819 women (aged 18-66) living in Melbourne, Australia. The presence of a coastline within 2 km of less educated women's homes explained 10.1% of the education-BMI relationship. These results suggest that beaches are also a good option for exercise, even among children and adults from low-income families.

In contrast with what was observed for parks/playgrounds, use of football pitches had a positive relationship with BMI and WC among low-income schoolchildren. These findings suggest reverse causality, thus indicating that low-income schoolchildren who have abdominal obesity use these places to exercise more. In fact, in Córdoba (Argentina) Lavin-Fueyo and Berra<sup>39</sup> observed that

**Table 4.** Crude and adjusted analysis on association between use of public places for physical activity and their distances from homes and waist circumference, according to family income strata, among 7 to 14-year-old schoolchildren living in Florianópolis, Santa Catarina, Brazil, 2012-2013

Environmental variables	Low income				Medium income				High income			
	Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>		Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>		Crude analyses <sup>a</sup>		Adjusted analyses <sup>*,a,b</sup>	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
<b>Uses beaches</b>												
No	0.00		0.00	-	0.00		0.00		0.00		-	-
Yes	-0.44	-1.39; 0.51	-	-	0.62	-0.56; 1.80	-0.02	-0.26; 0.22	-0.86	-2.57; 0.83	-	-
<b>Uses parks/ playgrounds</b>												
No	0.00		-	-	0.00		0.00		0.00		0.00	
Yes	<b>-1.05</b>	<b>-2.07; -0.03</b>	0.008	-0.11; 0.13	-0.81	-1.80; 0.16	0.02	-0.10; 0.15	<b>-1.49</b>	<b>-2.18; -0.80</b>	-0.23	-0.48; 0.03
<b>Uses sports courts</b>												
No	0.00		0.00		0.00		-	-	0.00		0.00	
Yes	0.47	-0.14; 1.08	0.08	-0.12; 0.29	0.68	-2.11; 3.48	-	-	<b>0.91</b>	<b>0.38; 1.44</b>	0.06	-0.16; 0.29
<b>Uses football pitches</b>												
No	0.00		-	-	0.00		0.00		0.00		0.00	
Yes	0.63	-0.92; 2.17	-	-	<b>1.19</b>	<b>0.76; 1.62</b>	0.05	-0.07; 0.18	1.17	-0.61; 2.95	0.04	-0.05; 0.15
<b>Distance to beaches (minutes)</b>												
1-10	0.16	-0.44; 0.78	-	-	-0.08	-1.86; 1.69	-	-	-0.61	-2.42; 1.19	-	-
11-19	0.73	-2.02; 3.49	-	-	-0.61	-1.99; 0.77	-	-	-0.38	-2.38; 1.60	-	-
≥ 20	0.00		-	-	0.00		0.00		0.00		-	-
<b>Distance to parks/playgrounds (minutes)</b>												
1-10	-0.15	-1.24; 0.93	-0.07	-0.27; 0.12	-0.03	-2.00; 1.93	-	-	0.21	-1.30; 1.74	-	-
11-19	<b>-1.23</b>	<b>-2.19; -0.26</b>	<b>-0.11</b>	<b>-0.17; -0.05</b>	0.73	-2.26; 3.73	-	-	0.47	-1.78; 2.73	-	-
≥ 20	0.00		0.00		0.00		0.00		0.00		-	-
<b>Distance to sports courts (minutes)</b>												
1-10	0.76	-1.44; 2.97	-	-	0.06	-1.62; 1.74	-	-	<b>1.34</b>	<b>0.46; 2.22</b>	-0.18	-0.44; 0.07
11-19	-0.24	-1.03; 0.54	-	-	0.12	-2.34; 2.58	-	-	<b>2.54</b>	<b>0.61; 4.50</b>	-0.20	-0.40; 0.00
≥ 20	0.00		-	-	0.00		0.00		0.00		0.00	
<b>Distance to football pitches (minutes)</b>												
1-10	0.48	-1.36; 2.33	0.07	-0.17; 0.25	0.26	-0.25; 0.78	-	-	1.10	-0.03; 2.24	-	-
11-19	0.36	-2.21; 2.93	<b>0.03</b>	<b>0.005; 0.14</b>	-0.16	-1.44; 1.11	-	-	<b>2.27</b>	<b>1.17; 3.37</b>	-	-
≥ 20	0.00		0.00		0.00		-	-	0.00		-	-

\*Multivariate models were controlled for the continuous variable of schoolchildren's age; <sup>a</sup>P-value significant at 5%; <sup>b</sup>Variables of use of and distance from football pitches presented collinearity.

the places for physical activity that schoolchildren from peripheral underprivileged neighborhoods used most were parks/public squares, in the first place, followed by football pitches. Another reason why we found a positive relationship between these variables could be that children and adolescent habitually go to football pitches to watch games, and this does not contribute towards improving their energy expenditure.

In our study, in the medium and higher-income strata, none of the environmental variables were associated with the outcomes in the adjusted analyses. One possible explanation for this is that in this socioeconomic stratum, other physical activity options, especially those that are supervised and consequently are not free of charge, may be used instead of public options. Bürgi et al.<sup>9</sup> in Zurich, Switzerland, observed that children living in neighborhoods with higher socioeconomic status did the majority of their moderate to intense physical activities in schools other than their own, possibly through taking part in paid-for exercise options.

It is also interesting to note that even though the variable of the distance from places for physical activity was associated with both outcomes, the variable of “use” of the same type of places was not statistically significant in any of the income strata in our study. In our sample, we found a significant positive relationship between frequency of use of places and their proximity to schoolchildren's homes (Table 2). Lavin-Fueyo et al.<sup>40</sup> used the same approach as in our study, to investigate the use of these places and their distances from homes. They investigated 1,777 children aged 9 to 11 years in the city of Córdoba, Argentina, in 2011, and also found that use of parks was associated with their proximity to schoolchildren's homes but was not associated with increases in the amount of physical activity. Among 22,889 adults evaluated in neighborhoods of Yorkshire, England, greater availability of parks within a distance of 2 km from home were associated both with lower BMI values and with lower prevalence of obesity.<sup>41</sup> In Louisiana, United States, the body profile of 909 women and their children was evaluated and it was found that living in a neighborhood with less provision of parks, playgrounds and other recreational places was significantly associated both with higher BMI and with larger WC, after adjusting for covariates.<sup>42</sup> These findings might indicate that the use of public spaces and open places for physical activities would be more frequent if these places are closer to home, and that maybe it is necessary to use them aiming to practice non-sedentary activities more than once a week, for there to be any positive effects regarding the intensity of physical activity and consequently regarding body profile. Such results are shown more frequently in adulthood.

The present study indicates that future analyses on the influence of the environment on physical activity and active leisure among children and adolescents living in medium-to-high income countries such as Brazil should take into account the economic inequalities affecting these populations, both at the family and at

the environmental level. One strong point of the present study is the fact that the sample was probabilistic and randomized, with a sample that was representative of schools in all five geographical regions in the municipal district studied. The weighting effect of each person in the sample was also taken into account (svy command), which minimized bias in the analysis on variables for which there were fewer responses. Interactions between the environmental variables were also analyzed (chi-square analyses), which reduced bias due to collinearity in multivariate models (we found collinearity between the variables of use of football pitches and distance from home to these places).

The primary limitation of this study was its cross-sectional design, which means that additional evidence is needed to support the findings. In addition, our study may have been affected by a cause-effect relationship among the variables, such that some schoolchildren who were using places for physical activity may have been doing so as part of a treatment for obesity. A situation of this nature would possibly hide a previously existing association with high body mass index and high measurements of waist circumference. Furthermore, we did not assess data on physical activity levels and food intake, because several variables could not be properly fitted into the multivariate models. Moreover, the correlation between the self-reported measurements of distances from schoolchildren's homes to the places with exercise facilities and objective measurements may not have been good. In such a situation, further studies regarding the feasibility of self-reported measurements for this issue would be required.

Our data indicate that there is a need to evaluate the relationship between the proximity of homes to places for PAAL and measurements of adiposity among the schoolchildren of Florianópolis in longitudinal studies, in order to confirm whether there is any direct relationship between the variables. If the findings from the present study are confirmed, it can be recommended that the public authorities responsible for urban planning of municipal districts should consider the need for creation of free public places for PAAL, especially in economically underprivileged areas, in order to encourage active behavior among their residents and prevent the emergence of overweight and obesity among children and adolescents in low-income groups.

## CONCLUSION

This study identified a significant association between proximity of parks/playgrounds to homes and lower BMI and WC values, and an association between short distances from homes to football pitches and higher BMI and WC among schoolchildren in low-income groups who were living in Florianópolis. An intermediate distance from homes to beaches was also associated with lower BMI values among schoolchildren from low-income families.

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# Social, behavioral and biological correlates of cardiorespiratory fitness according to sex, nutritional status and maturity status among adolescents. A cross-sectional study

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## KEY WORDS:

Physical fitness.  
Adolescent health.  
Motor activity.  
Social class.

## ABSTRACT

**BACKGROUND:** Our aim was to analyze multilevel correlates of cardiorespiratory fitness (CRF) according to sex, nutritional status and maturity status among adolescents.

**DESIGN AND SETTING:** Cross-sectional study conducted in public schools.

**METHODS:** This was a cross-sectional study on 1,209 adolescents aged between 10 and 17 years. CRF was estimated from the 20-meter shuttle run test. Anthropometric data on body mass index and waist circumference were obtained. Somatic maturation was assessed from the peak height velocity. Questionnaires were used to evaluate socioeconomic variables (family income, parents' education level and number of siblings) and behavioral variables (physical activity, screen time and alcohol and tobacco consumption) among the parents and adolescents.

**RESULTS:** Boys, adolescents with normal weight and on-time maturers presented greater CRF ( $P < 0.05$ ). Concerning socioeconomic correlates, girls (tobacco smoking, alcohol consumption, physical activity and screen time), adolescents with normal weight (alcohol consumption, physical activity and screen time), and on-time maturers (alcohol consumption, physical activity during childhood and habitual physical activity) demonstrated higher numbers of behavioral correlates with CRF. Normal-weight adolescents presented a higher number of biological correlates (chronological age, age at peak height velocity and waist circumference).

**CONCLUSIONS:** Different correlates were observed according to sex, nutritional status and somatic maturation status. However, habitual physical activity, waist circumference and chronological age seemed to be the strongest factors associated with cardiorespiratory fitness among adolescents.

## INTRODUCTION

Cardiorespiratory fitness measured during physical effort is the ability to provide oxygen effectively to skeletal muscles,<sup>1</sup> which is recognized as a protective factor against obesity,<sup>2</sup> cardiovascular risk<sup>3,4</sup> and mortality.<sup>5</sup> This capacity seems to be active from early ages to adulthood,<sup>6</sup> thus highlighting the importance of promoting adequate levels of this physical fitness component from infancy onwards. Therefore, understanding possible factors associated with cardiorespiratory fitness (i.e. correlates) among children and adolescents is relevant for development of effective interventions to improve this factor.

Variables that correlate with cardiorespiratory fitness during adolescence can be grouped into different "levels" based on their proximity to cardiorespiratory fitness. Firstly, there are socioeconomic and parental environmental factors, such as socioeconomic status, parental educational status and physical activity relating to cardiorespiratory fitness.<sup>7</sup> In addition, there are behavioral associated factors, such as physical activity, sedentary behavior and others.<sup>7</sup> Finally, close to cardiorespiratory fitness, there are biological associated factors such as fatness<sup>2</sup> and chronological age.<sup>8</sup>

Specifically regarding biological factors, it can be expected that cardiorespiratory fitness will increase over the growth process.<sup>9</sup> The rate of growth (biological maturation) can influence cardiorespiratory fitness directly, through development of cardiovascular and respiratory systems,<sup>10</sup> as well as having an important role in several psychological and behavioral factors.<sup>11</sup> Thus, biological maturation seems to be a key correlate during adolescence. Moreover, body composition is also strongly associated with cardiorespiratory fitness in this age group<sup>12</sup> and may confound association results if not considered.<sup>13</sup>

Our aim in the present study was to analyze social, behavioral and biological correlates of cardiorespiratory fitness according to sex, nutritional status and maturity status, through a multilevel approach, among Brazilian adolescents. The initial hypothesis of the study was that sex, nutritional status and maturity status would be strongly associated with cardiorespiratory fitness<sup>3</sup> and would have a role in several of its associated factors at different levels. These would include biological factors (e.g. waist circumference), behavioral factors (e.g. tobacco smoking, alcohol consumption, physical activity and screen time) and social factors (e.g. socioeconomic status, parental variables and number of siblings). In this manner, different correlates of physical activity would exist according to these biological constructs (boys versus girls; normal weight versus overweight/obese; and late versus on-time versus early maturity).

## METHODS

### Sample

This was a cross-sectional study conducted among Brazilian adolescents aged between 10 and 17 years who were enrolled in public schools. The city of Londrina, Paraná, where the study was conducted, has a medium human development index.<sup>14</sup> The current study forms part of a project entitled "Prevalence of metabolic syndrome and cardiovascular risk factors in adolescents from Londrina" for which the sample size calculation was based on the following parameters: prevalence of metabolic syndrome of 4%;  $\alpha$  of 0.05; margin of error of two percentage points; and design effect of 2.0. The sample size was further increased by 20% to compensate for any participant withdrawals. Following the recommendation of Luiz and Magnanini,<sup>14</sup> at least 900 adolescents should be recruited.

Sample recruitment was performed in two stages. First, all public schools in the city were separated into regions (north, south, east, west and central) and two schools were randomly selected from each region. Subsequently, two or three classes were randomly identified in each school and all students within these classes (except those using prescription medicine or undergoing treatment for an illness) were invited to participate in the study. Students failing to return a consent form signed by their parents were considered ineligible. The total number of adolescents recruited was 1,395; however, due to missing data, especially parental data, the final sample was composed of 1,209 adolescents (549 boys and 660 girls).

Reassuringly, it was demonstrated that these participants with complete data were representative of all the adolescents who were initially enrolled in the study.<sup>4</sup> Moreover, all the questionnaires were reapplied to a subsample of 129 adolescents from the pilot study, who were not included in the final sample of this article, with the aim of calculating intraclass coefficients.

The local ethics committee approved all the study procedures, which adhered to the principles of the Declaration of Helsinki (procedural number 10655/2012).

### Cardiorespiratory fitness

The 20-meter shuttle run test<sup>15</sup> was administered in sports courts and was used to define maximal aerobic speed and consequently to estimate cardiorespiratory fitness. Subsequently, peak oxygen consumption, in  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , was estimated according to the equation 1 proposed by Leger et al.<sup>16</sup>

$$\text{VO}_2 \text{ peak} = 31.025 + 3.238 \cdot S - 3.248 \cdot A + 0.1536 \cdot S \cdot A \quad (1)$$

Where:

S = final speed ( $\text{kmh}^{-1}$ );

A = age (years).

### Biological maturation and nutritional status

Biological maturation was estimated through the somatic maturation method derived from the estimated age at peak height velocity, as proposed by Mirwald et al.<sup>17</sup> This method estimates distance in years from peak height velocity through anthropometric variables (height, seated height, leg length and body mass). Predictions for age at peak height velocity are determined through subtracting the maturity offset from chronological age. For categorization, we used the method of standard deviations (sd) derived from the sample (late:  $> +1$  sd; on time:  $+/- 1$  sd; early:  $< 1$  sd).

Maturity offset for boys (in years) =  $-9.236$

- $+ [0.0002708 \cdot (\text{leg length} \cdot \text{seated height})]$
- $+ [-0.001663 \cdot (\text{age} \cdot \text{leg length})]$
- $+ [0.007216 \cdot (\text{age} \cdot \text{seated height})]$
- $+ [0.02292 \cdot (\text{body mass/height} \cdot 100)]$

Maturity offset for girls (in years) =  $-9.376$

- $+ [0.0001882 \cdot (\text{leg length} \cdot \text{seated height})]$
- $+ [0.0022 \cdot (\text{age} \cdot \text{leg length})]$
- $+ [0.005841 \cdot (\text{age} \cdot \text{seated height})]$
- $+ [0.002658 \cdot (\text{age} \cdot \text{body mass})]$
- $+ [0.07693 \cdot (\text{body mass/height} \cdot 100)]$

### Body mass index and waist circumference

Body mass was accessed using a digital scale (Balmak; precision = 0.1 kg) and height was measured using a stadiometer with precision of 0.01 cm, in accordance with standardized procedures in the literature.<sup>18</sup> Nutritional status was estimated through the body mass index (BMI) using the formula:  $\text{body mass (kg)/height (m)}^2$ , with the following values for technical errors of measurement: weight = 0.68% and height = 0.37%. Waist circumference was measured between the rib cage and the iliac crest (minimum circumference), as recommended in the literature,<sup>19</sup> using an anthropometric tape

with a precision of 0.1 cm. All the procedures were performed while the adolescent subjects were wearing light clothing.

### Parental/socioeconomic factors

Data on the parents' tobacco smoking and alcohol consumption were collected through a self-report questionnaire, with dichotomous questions (yes or no), which were answered by the parents of the adolescents. We made the following assumptions regarding the data:

1. We considered the parents to be alcohol consumers if they reported using alcohol at least once a week in answer to the question: "How often do you drink alcoholic drinks?"
2. Similarly, we considered the parents to be tobacco smokers if they reported using tobacco in answer to the question: "Do you have a tobacco smoking habit?"
3. Physical activity levels were self-reported using the Baecke questionnaire, which captures information regarding exercise practice and duration of practice. In line with physical activity guidelines,<sup>20</sup> parents who reported being physically active for more than 180 minutes/week were classified as active.
4. Maternal and paternal BMI were calculated using self-reported values for weight and height in response to questionnaires that were answered by each parent. Previous studies had reported good validity of self-reported body size data among Brazilian adults.<sup>21</sup>

### Behavioral factors

The behavioral factors were defined as follows:

1. Information on alcohol consumption and tobacco smoking among the adolescents was obtained in a dichotomous manner (yes or no), through indication of the use during the previous 30 days. For quality control, the intraclass correlation coefficients (ICCs) for a repeated pilot sample for alcohol consumption and tobacco smoking were respectively 0.74 and 0.78.
2. The Baecke questionnaire<sup>22</sup> was applied to estimate habitual physical activity and the score proposed by the authors of the original study were taken to be an indicator of habitual physical activity (ICC = 0.73).
3. Physical activity during early life was estimated through a question asking about sports practice during childhood. This question is used in the literature.<sup>23,24</sup>
4. Adolescents who reported doing systematized exercise (practicing a structured program of exercise under supervision from a coach) for at least one year were considered to have been active during childhood.
5. Screen time (ICC = 0.77) in minutes per week and at the weekend was taken to be an indicator of sedentary behavior.

### Statistical analysis

Frequencies, means and standard deviations were used to compare groups, along with the Kruskal-Wallis test (for somatic maturity status) and the Mann-Whitney test (regarding sex and nutritional

status). Partial correlations (adjusted according to sex) between three levels of correlates and cardiorespiratory fitness were used. The correlation coefficients were interpreted as follows: trivial ( $r < 0.1$ ), small ( $0.1 > r < 0.3$ ), moderate ( $0.3 > r < 0.5$ ), large ( $0.5 > r < 0.7$ ), very large ( $0.7 > r < 0.9$ ), nearly perfect ( $r > 0.9$ ) and perfect ( $r = 1$ ). To test the association between correlates and cardiorespiratory fitness, hierarchical linear regression was conducted as described by Victora et al.,<sup>25</sup> with three blocks of variables that were entered in the following order:

1. parental and socioeconomic-related variables;
2. behavioral variables; and
3. biological variables.

All analyses were performed using the SPSS software (version 23.0) with a significance level of  $P < 0.05$ .

### RESULTS

Boys presented greater habitual physical activity and screen time than girls ( $P < 0.001$ ). Moreover, regarding biological variables, boys, normal-weight adolescents and late-maturing adolescents presented higher means for chronological age, age at peak height velocity and waist circumference (Table 1). On-time maturing adolescents presented higher cardiorespiratory fitness than late-maturing adolescents ( $P = 0.027$ ) (Figure 1).

Partial correlations between associated factors (hierarchically divided into three levels, i.e. parental and socioeconomic-related variables, behavioral variables and biological variables) and cardiorespiratory fitness according to sex, nutritional status and somatic maturity status are presented in Table 2.

Among boys, their mother's educational status (low magnitude), their physical activity levels (low magnitude) and waist circumference (moderate magnitude) were related to cardiorespiratory fitness. On the other hand, girls with lower socioeconomic status (trivial magnitude), whose mothers were active (trivial magnitude), did not smoke tobacco (small magnitude) or drink alcohol (small magnitude), and who had higher habitual physical activity (small magnitude) and lower screen time (small magnitude), presented higher cardiorespiratory fitness. Regarding peak height velocity, girls who were more advanced in maturation presented higher cardiorespiratory fitness (small magnitude). The adolescents of both sexes with smaller waist circumference presented higher cardiorespiratory fitness (moderate magnitude) (Table 2).

Concerning associations according to nutritional status, normal-weight and overweight/obese adolescents presented positive correlations between early and habitual physical activity and cardiorespiratory fitness. Conversely, both groups also presented negative correlations between chronological age and waist circumference and cardiorespiratory fitness. In the specific analysis on normal-weight adolescents, higher cardiorespiratory fitness was associated with socioeconomic status (trivial correlation), more siblings (trivial correlation), not drinking alcohol (trivial correlation) and age at

peak height velocity (small correlation), while among overweight/obese adolescents, higher cardiorespiratory fitness was associated with lower paternal nutritional status (small correlation) and non-consumption of tobacco (small correlation) (Table 2).

When divided according to somatic maturity status, cardiorespiratory fitness in all three groups was positively associated with habitual physical activity and age at peak height velocity and negatively associated with waist circumference. In late-maturing adolescents, cardiorespiratory fitness was associated with early physical activity (small correlation), lower chronological age (moderate correlation), not smoking tobacco (small correlation) and number of siblings (small correlation). On the other hand, in on-time maturing adolescents,

cardiorespiratory fitness was associated with early physical activity (small correlation) and lower chronological age (small correlation) (Table 2). Table 3 summarizes the linear regression (significant variables) with the objective of obtaining possible correlates.

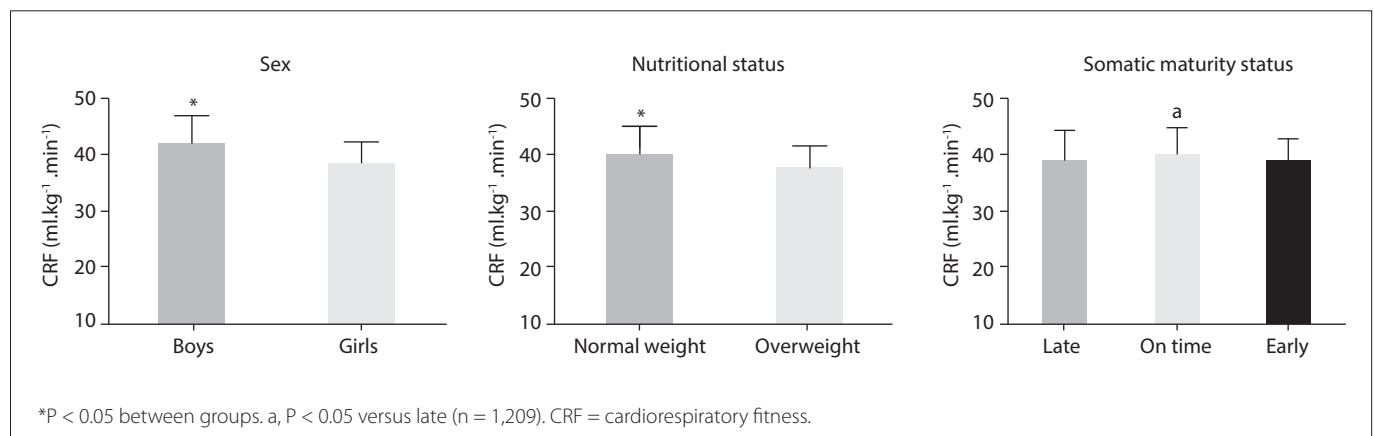
## DISCUSSION

Our aim was to analyze correlates of cardiorespiratory fitness in three levels (parental and socioeconomic-related variables, behavioral variables and biological variables) according to sex, nutritional status and somatic maturity status. To our knowledge, this is the first study that considered this range of associated factors in three levels stratified according to sex, nutritional status

**Table 1.** Characteristics of the sample according to hierarchical levels, sex, nutritional status and somatic maturity status

	Sex		Nutritional status		Somatic maturity status		
	Boys (n = 549)	Girls (n = 660)	Normal weight (n = 958)	Overweight/obese (n = 251)	Late (n = 168)	On time (n = 871)	Early (n = 170)
Chronological age (years)	13.0 ± 1.5*	12.8 ± 1.4	12.9 ± 1.5*	12.6 ± 1.4	14.3 ± 1.4*	12.8 ± 1.3	12.0 ± 1.1
Age at peak height velocity (years)	14.4 ± 0.7*	12.4 ± 0.7	13.4 ± 1.2*	12.8 ± 1.2	14.4 ± 1.0*	13.3 ± 1.1	12.2 ± 1.0
Waist circumference (cm)	67.7 ± 9.0*	65.5 ± 7.9	63.4 ± 5.3*	78.2 ± 8.2	64.3 ± 6.3	65.5 ± 7.8	73.8 ± 10.1 <sup>†</sup>
Tobacco smoking (%)	8.4%	8.2%	7.6%	8.5%	15.5%*	6.9%	4.5%
Alcohol consumption (%)	18.8%	17.9%	18.1%	15.8%	23.2%*	17.4%	12.8%
Early physical activity (%)	74.0%*	60.0%	65.4%	70.2%	62.4%	67.5%	64.8%
Habitual physical activity (score)	8.5 ± 1.4*	7.7 ± 1.3	8.1 ± 1.4	8.0 ± 1.5	8.0 ± 1.5	8.1 ± 1.4	7.9 ± 1.4
Screen time (hours)	8.7 ± 5.8*	7.7 ± 4.7	8.2 ± 5.1	8.1 ± 4.9	8.1 ± 4.9	8.2 ± 5.4	7.7 ± 4.7
Socioeconomic status (low) (%)	65.5%	68.3%	67.3%	66.4%	73.8%	65.7%	67.4%
Maternal educational status <sup>1</sup> (%)	33.8%	24.3%	26.4%	25.2%	19.0%	27.3%	27.6%
Paternal educational status <sup>1</sup> (%)	32.4%	25.8%	27.8%	29.4%	21.9%	29.1%	29.4%
Maternal tobacco smoking (%)	14.1%	16.0%	15.6%	12.5%	15.0%	15.7%	11.0%
Paternal tobacco smoking (%)	27.3%	29.7%	28.6%	27.6%	30.0%	28.5%	26.0%
Maternal alcohol consumption (%)	21.7%	25.1%	24.7%	18.4%	33.0%	24.5%	18.0%
Paternal alcohol consumption (%)	52.1%	53.8%	55.1%	55.4%	60.0%	53.0%	46.0%
Maternal body mass index (kg/m <sup>2</sup> )	26.7 ± 5.5	26.4 ± 5.2	26.3 ± 5.3	27.6 ± 5.4	25.9 ± 5.3	26.6 ± 5.3	27.0 ± 5.5
Paternal body mass index (kg/m <sup>2</sup> )	26.5 ± 4.6	26.3 ± 4.3	26.1 ± 4.1*	27.3 ± 4.9	26.4 ± 3.8	26.1 ± 4.3	27.8 ± 4.9 <sup>†</sup>
Maternal physical activity (%)	4.3%	2.5%	3.0%	3.9%	5.0%	2.7%	4.0%
Paternal physical activity (%)	7.2%	6.8%	6.5%	7.9%	4.0%	7.3%	7.0%
Number of siblings (n)	2.5 ± 1.9	2.6 ± 2.1	2.6 ± 2.0	2.2 ± 1.8	2.9 ± 2.0	2.5 ± 1.9	2.4 ± 2.0

\*P < 0.05 for trend or differences between all groups. <sup>†</sup>denotes significant difference compared to "on time" in somatic maturity status.



**Figure 1.** Cardiorespiratory fitness according to sex, nutritional status and somatic maturity status.

and maturity status. The main findings of the present study indicate that there are correlates of cardiorespiratory fitness at different levels, and that there are different correlates according to sex, nutritional status and maturity status. Greater numbers of correlates were observed among girls, normal-weight adolescents and on-time maturing adolescents. Furthermore, the correlates that appeared more frequently among the models were habitual physical activity, waist circumference and chronological age.

Boys tend to present higher values for cardiorespiratory fitness because of their biological and behavioral characteristics, especially after the biological maturation process, since boys have greater muscle mass, which is associated with cardiorespiratory fitness.<sup>2,9,26</sup> Moreover, boys have higher levels of physical activity than girls, which is related to cardiorespiratory fitness.<sup>7</sup> This finding corroborates other studies and can also be explained by the built environment, in which boys receive greater incentive to practice physical activity.<sup>27,28</sup> Similarly, nutritional status has a role in estimating cardiorespiratory fitness, such that because of the growth process, cardiorespiratory fitness seems to be underestimated among overweight/obese adolescents.<sup>16</sup> Concerning biological maturation, it can be expected that cardiorespiratory fitness will increase over the course of the maturation process, also due to changes in muscle mass and evolution in organic systems.<sup>8</sup>

We found that only the mother's educational status, number of siblings, habitual physical activity and waist circumference were

associated with cardiorespiratory fitness among boys. On the other hand, the number of associated factors was higher among girls: these were mainly behavioral correlates (habitual physical activity, tobacco smoking, alcohol consumption and screen time). This could be because cardiorespiratory fitness is more affected by biological variables in boys than in girls,<sup>2</sup> while female cardiorespiratory fitness is more affected by behavioral variables. Moreover, the correlates among boys were stronger and, consequently, fewer than among girls, thus indicating that a greater range of possible interventions aiming towards improvement of cardiorespiratory fitness exists for girls, while more specific correlates are necessary among boys.

A similar point of view can be applied to our results relating to nutritional status. Normal-weight adolescents presented higher values for cardiorespiratory fitness and higher numbers of significant correlates than did overweight/obese adolescents. This could be due to the relationship between adiposity and cardiorespiratory fitness,<sup>30</sup> which presented a strong relationship in our models for overweight/obese adolescents and overlapped with other correlates.

Furthermore, late-maturing adolescents presented only maternal physical activity, habitual physical activity and chronological age as correlates; on-time adolescents presented a broad range of behavioral correlates; and early maturers presented significant correlates with the number of siblings, habitual physical activity and waist circumference. Given our hypothesis, correlates may change

**Table 2.** Partial correlations between independent variables and cardiorespiratory fitness according to sex, nutritional status and maturity status (n = 1,209)

	Sex		Nutritional status		Somatic maturity status		
	Boys	Girls	Normal weight	Overweight/obese	Late	On time	Early
<b>First level</b>							
Socioeconomic status	-0.017	<b>-0.092</b>	<b>0.077</b>	0.065	-0.126	-0.007	-0.072
Maternal educational status	<b>-0.108</b>	-0.025	-0.020	-0.090	0.006	-0.055	-0.073
Paternal educational status	-0.084	-0.052	-0.004	-0.037	0.058	-0.039	-0.068
Maternal tobacco smoking	0.074	0.041	0.039	0.019	0.090	0.017	-0.073
Paternal tobacco smoking	0.005	0.059	0.040	-0.107	-0.045	0.012	-0.068
Maternal alcohol consumption	0.031	0.007	-0.013	0.014	0.073	-0.012	-0.015
Paternal alcohol consumption	0.015	0.033	0.005	0.129	0.140	0.026	-0.006
Maternal body mass index	0.008	-0.056	0.049	-0.141	-0.050	0.007	-0.047
Paternal body mass index	-0.103	-0.074	0.004	<b>-0.209</b>	0.028	-0.079	-0.052
Maternal physical activity status	0.046	<b>0.097</b>	0.052	0.144	0.154	0.045	0.040
Paternal physical activity status	0.006	0.020	0.026	0.033	0.070	0.029	-0.082
Number of siblings	<b>0.106</b>	0.067	<b>0.077</b>	-0.062	<b>0.164</b>	0.051	0.151
<b>Second level</b>							
Tobacco smoking	0.022	<b>-0.180</b>	-0.049	<b>-0.153</b>	<b>-0.198</b>	0.001	-0.055
Alcohol consumption	-0.044	<b>-0.118</b>	<b>-0.068</b>	-0.078	-0.098	-0.065	0.110
Early physical activity	<b>0.123</b>	<b>0.080</b>	<b>0.174</b>	<b>0.158</b>	<b>0.221</b>	<b>0.144</b>	0.102
Habitual physical activity	<b>0.224</b>	<b>0.180</b>	<b>0.323</b>	<b>0.215</b>	<b>0.369</b>	<b>0.286</b>	<b>0.326</b>
Screen time	-0.016	<b>-0.158</b>	-0.047	0.039	-0.082	-0.032	0.065
<b>Third level</b>							
Chronological age	<b>-0.172</b>	<b>-0.533</b>	<b>-0.325</b>	<b>-0.360</b>	<b>-0.351</b>	<b>-0.287</b>	-0.072
Age at peak height velocity	0.021	<b>-0.237</b>	<b>0.281</b>	0.034	<b>0.419</b>	<b>0.349</b>	<b>0.309</b>
Waist circumference	<b>-0.403</b>	<b>-0.356</b>	<b>-0.130</b>	<b>-0.250</b>	<b>-0.246</b>	<b>-0.307</b>	<b>-0.460</b>

The values in bold indicate  $P < 0.05$ . Adjusted according to sex.

between maturity categories because of their intrinsic biological and psychological alterations.<sup>11</sup> Chronological age probably entered the late-maturing model due to the lack of more advanced maturation of systems.<sup>10</sup> On the other hand, age did not enter the early-maturing model because the prevalence of obesity among early-maturing adolescents is high and therefore waist circumference would seem to be a better predictor of cardiorespiratory fitness.

In general, we found correlates of cardiorespiratory fitness among all three theoretical levels. In the first level, cardiorespiratory fitness was inversely related to two indicators of socioeconomic status (maternal educational level and socioeconomic status). This phenomenon seems to occur especially through the possible influence of socioeconomic status on some behaviors,<sup>31</sup> consequently influencing cardiorespiratory fitness. In addition, we found that home environmental correlates were also associated with cardiorespiratory fitness (paternal nutritional status, maternal physical activity levels and number of siblings), which would indicate possible social influence and transfer of behaviors between people who live together.<sup>32</sup>

Although a large part of cardiorespiratory fitness can be explained biologically,<sup>33</sup> healthy behaviors also have an effect. The most consistent association that we found was with physical activity, which has a clear effect, especially in the exercise domain.<sup>34</sup> Contrary to the well-recognized beneficial effects of physical exercise, we also found that drinking alcohol and smoking tobacco had an adverse effect on cardiorespiratory fitness, which is consistent, given their deleterious effects on health.<sup>35</sup> Moreover, early physical activity can have a particular role, even genetically.<sup>36</sup> Screen time is also a negative form of behavior, especially because of the lack of muscle contractions. In addition to the independent effects of each of these behaviors, they may interact, given that they are correlated.<sup>37</sup>

Biological factors are closer to the outcome, given that this is also biological.<sup>7</sup> In this regard, we found that cardiorespiratory fitness increased with chronological age. This occurs because several biological developmental processes occur during growth.<sup>9</sup> Similarly, biological maturation affects cardiorespiratory fitness, although it can influence both biological and behavioral correlates.<sup>11</sup>

**Table 3.** Hierarchical regression models of correlates of cardiorespiratory fitness according to sex, nutritional status and maturity status (n = 1,209)

	Sex		Nutritional status		Somatic maturity status		
	Boys	Girls	Normal weight	Overweight/obese	Late	On time	Early
<b>First level</b>							
<b>Adjusted R<sup>2</sup></b>	0.012	0.015	0.216	0.095	0.263	-	0.112
Socioeconomic status	-	-0.34 (-0.63 to -0.04)	-	-	-	-	-
Maternal educational status	-0.46 (-0.87 to -0.04)	-	-	-	-	-	-
Paternal body mass index	-	-	-	-0.14 (-0.268 to -0.029)	-	-	-
Maternal physical activity status	-	2.38 (0.41 to 4.34)	-	-	4.57 (0.686 to 8.462)	-	-
Number of siblings	-	-	0.195 (0.058 to 0.331)	-	-	-	0.297 (0.040 to 0.555)
<b>Second level</b>							
<b>Adjusted R<sup>2</sup></b>	0.081	0.104	0.280	0.149	0.307	0.203	0.165
Tobacco smoking	-	-2.65 (-4.12 to -1.18)	-	-2.92 (-5.494 to -0.354)	-	-	-
Alcohol consumption	-	-0.92 (-1.83 to -0.01)	-1.372 (-2.115 to -0.629)	-	-	-1.249 (-2.049 to -0.449)	-
Early physical activity	-	-	-	1.51 (0.278 to 2.749)	-	0.671 (0.011 to 1.330)	-
Habitual physical activity	0.93 (0.59 to 1.27)	0.44 (0.18 to 0.71)	0.705 (0.492 to 0.918)	-	1.10 (1.499 to 1.703)	0.515 (0.278 to 0.752)	0.619 (0.207 to 1.032)
Screen time	-	-0.14 (-0.21 to -0.07)	-0.099 (-0.155 to -0.044)	-	-	-	-
<b>Third level</b>							
<b>Adjusted R<sup>2</sup></b>	0.246	0.333	0.401	0.253	0.458	0.365	0.425
Chronological age	-	-1.54 (-1.80 to -1.28)	-0.854 (-1.134 to -0.574)	-0.548 (-0.987 to -0.108)	-1.53 (-2.085 to -0.994)	-0.545 (-0.771 to -0.319)	-
Age at peak height velocity	-	0.70 (0.19 to 1.21)	-0.675 (-1.230 to -0.121)	-	-	-	-
Waist circumference	-0.22 (-0.27 to -0.17)	-	-0.080 (-0.150 to -0.010)	-0.120 (-0.191 to -0.050)	-	-0.199 (-0.239 to -0.159)	-0.192 (-0.238 to -0.146)

Non-significant models are not presented; P < 0.05; Adjusted according to sex.

Although biologically early-maturing adolescents may present higher physical fitness, they also have greater likelihood of presenting unhealthy behaviors<sup>11,38</sup> that can influence health outcomes.

The three levels of correlates indicate different types of interventions, as well as risk groups. According to our results, older adolescents, girls and adolescents with greater waist circumference should receive special attention. Moreover, family-based interventions and behavioral interventions among adolescents appear to be interesting interventions for increasing cardiorespiratory fitness<sup>33,39</sup>

Our study presents some limitations that need to be acknowledged. Firstly, our measurement of parental characteristics was through self-reporting and may have presented bias, although self-reports among adults have demonstrated good validity.<sup>20</sup> Moreover, both physical activity and early physical activity were estimated through questionnaires, which despite the possibility of presenting bias, showed good reproducibility (ICC = 0.73). On the other hand, we used an indirect, but valid method of estimation of cardiorespiratory fitness that has been widely used in the literature.<sup>3,7,8,14</sup> Finally, because of our study design (cross-sectional), we cannot indicate the causality between exposures and outcome.

## CONCLUSIONS

In summary, we confirmed that there are correlates of cardiorespiratory fitness at different levels of variables (social, behavioral and biological). Among the associated factors tested, habitual physical activity, waist circumference and chronological age seem to be strongly associated with cardiorespiratory fitness, even though different correlates were found according to sex, nutritional status and somatic maturation status.

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# Coarse particles and hospital admissions due to respiratory diseases in children. An ecological time series study

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## KEY WORDS:

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## ABSTRACT

**BACKGROUND:** Exposure to particulate matter (PM) is associated with hospitalizations due to respiratory diseases among children.

**DESIGN AND SETTING:** An ecological time series study was carried out to identify the role of coarse fractions of particulate matter (PM<sub>10-2.5</sub>) in hospitalizations among children up to 10 years of age, in Piracicaba (SP) in the year 2015.

**METHODS:** A generalized additive model of Poisson regression was used to estimate the risk of hospitalization due to acute laryngitis and tracheitis, pneumonia, bronchitis, bronchiolitis and asthma. Lags of 0 to 7 days were considered, and the model was adjusted for the temperature and relative humidity of the air and controlled for short and long-term exposure. Proportional attributable ratios, population-attributable fractions and hospital costs were calculated with increasing concentrations of these pollutants.

**RESULTS:** 638 hospitalizations were evaluated during this period, with a mean of 1.75 cases per day (standard deviation, SD = 1.86). The daily averages were 22.45 µg/m<sup>3</sup> (SD = 13.25) for the coarse fraction (PM<sub>10-2.5</sub>) and 13.32 µg/m<sup>3</sup> (SD = 6.38) for the fine fraction. Significant risks of PM<sub>10-2.5</sub> exposure were only observed at lag 0, with relative risk (RR) = 1.012, and at lag 6, with RR = 1.011. An increase of 5 µg/m<sup>3</sup> in the coarse fraction concentration implied an increase in the relative risk of hospitalizations of up to 4.8%, with an excess of 72 hospitalizations and excess expenditure of US\$ 17,000 per year.

**CONCLUSIONS:** This study showed the impact of coarse-fraction exposure on hospital admissions among children due to respiratory diseases.

## INTRODUCTION

Air pollution is estimated to be directly responsible for more than two million deaths per year worldwide, caused by damage to the lungs and respiratory tract. A large proportion of the morbidity and mortality due to respiratory diseases is caused by exposure to particulate matter (PM).<sup>1,2</sup>

Particulate matter with an aerodynamic diameter of less than 10 µm (PM<sub>10</sub>) is composed of solid and liquid particles suspended in the air. It varies in size and chemical composition and is able to carry adsorbed chemicals, biological material and metals on its surface. The effects of exposure to fine particulate matter on health, particularly with regard to hospitalizations due to respiratory diseases, have been described in some studies.<sup>3-9</sup>

The particles in PM<sub>10</sub> are further classified based on their capacity for lung penetration, as follows: fine (PM<sub>2.5</sub>) if their diameter is not more than 2.5 µm; and coarse (PM<sub>10-2.5</sub>) if their diameter is between 2.5 µm and 10 µm. For the latter fraction, which is commonly formed by mechanical grinding and resuspension of solid material, no specific standard for air quality analysis has been adopted, and the general PM<sub>10</sub> standard is used.<sup>2</sup>

However, recently, the difference between coarse and fine particles has become more explicitly appreciated. Separate measurements of fine-particle (PM<sub>2.5</sub>) concentration and coarse-particle (PM<sub>10-2.5</sub>) concentration have been included in studies, rather than measurements of PM<sub>2.5</sub> and PM<sub>10</sub>. This has shown that, in contrast to the high correlation between PM<sub>10</sub> concentration and PM<sub>2.5</sub> concentration, there is often much less correlation between PM<sub>2.5</sub> concentration and PM<sub>10-2.5</sub> concentration. It should be noted that coarse-particle concentration is usually obtained by subtracting a direct measurement of PM<sub>2.5</sub> concentration from a direct measurement of PM<sub>10</sub> concentration.<sup>10</sup>

In toxicological studies, some evidence that the coarse fraction may be more inflammatory than  $PM_{2.5}$  has been reported.<sup>11-13</sup> According to Adar et al.,<sup>2</sup> the health implications of exposure to the coarse fraction are still poorly understood, given that most research has focused on fine particles.

The objective of this study was to investigate the association between exposure to the coarse fraction of particulate matter and hospitalizations due to respiratory diseases among children up to 10 years of age living in Piracicaba (SP).

## METHODS

### Study design

An ecological time series study on children from zero to 10 years of age living in Piracicaba was conducted from January 1, 2015, to December 31, 2015. Daily indicators of hospitalization due to respiratory diseases were gathered, including data on acute laryngitis and tracheitis, pneumonia, bronchitis, bronchiolitis and asthma, using the International Classification of Diseases (ICD) 10<sup>th</sup> revision (J04, J12-J18, J20-J21 and J45). These data were obtained from the Department of Informatics of the Brazilian National Health System (Departamento de Informática do Sistema Único de Saúde, DATASUS).<sup>14</sup>

The study used data from the municipality of Piracicaba (SP). This municipality, located at the coordinates 22° 43' S and 47° 39' W, at an altitude of 547 meters, is considered to be of medium size and covers approximately 1,400 km<sup>2</sup>. Its estimated population in 2016 was around 400,000 inhabitants. Its vehicle fleet was estimated to be around 250,000 cars, trucks and motorcycles and 13,000 buses in 2015.<sup>15</sup> Piracicaba is an important city in the sugar and alcohol industry, which means that pollutants in this region come not only from burning of fuel in vehicles but also from burning of straw from sugarcane production.

The mean temperature and relative humidity of the municipality were obtained from the website of the Environmental Sanitation Company of the State of São Paulo (Companhia Ambiental do Estado de São Paulo, CETESB).<sup>16</sup>

The 24-hour average concentrations of the pollutants  $PM_{2.5}$  and  $PM_{10}$  were used to calculate the coarse fraction. Thus, the coarse fraction ( $PM_{10-2.5}$ ) was obtained by subtracting the  $PM_{2.5}$  concentration from the  $PM_{10}$  concentration.

### Statistical analysis

Descriptive analyses on the daily average, minimum and maximum values, standard deviation of the study variables and the respective percentage values for pollutants, in accordance with the  $PM_{10}$  concentration, were presented in table form. Pearson's correlation test was used to evaluate the possible correlations between hospitalizations and daily levels of pollutants ( $PM_{2.5}$  and coarse fraction).

To investigate these effects, the generalized Poisson regression additive model (GAM) was used. In this, each pollutant was analyzed separately (unipollutant model), with adjustments for mean temperature, relative humidity, short-term exposure and long-term seasonality of exposure.

Since the effects of exposure to air pollutants can lead to hospitalization on the same day as exposure (lag 0) or on days subsequent to exposure, the impacts on the respiratory tract on the day of hospitalization (lag 0) and on the subsequent seven days (lag 1 to lag 7) were investigated.

To calculate the relative risk (RR) of hospitalizations, calculated with a 95% confidence interval, increments of 5  $\mu\text{g}/\text{m}^3$  were chosen for each pollutant, using the formula:  $RR = [\exp(5 \times \beta)]$ , where  $\beta$  is the value of the coefficient provided by the adjusted regression model for each pollutant.

The concepts of proportional attributable risk (PAR) and population-attributable fraction (PAF) were used to estimate the excess hospitalizations due to the increase in the concentrations of the fine and coarse fractions of the particulate material.

PAR is expressed through the equation  $PAR = [1 - 1/RR]$ , where RR is the relative risk; and PAF is expressed through the equation  $PAF = [PAR(\%) \times N]$ , where N is the total population studied. The mean hospital admission costs relating to respiratory diseases were obtained from DATASUS.<sup>14</sup>

The Statistica 7 software (StatSoft, Inc., Tulsa, OK, USA) and a 5% significance level were used for these analyses.

This project was approved by the Research Ethics Committee of the University of Taubaté, under number 314/04.

## RESULTS

A total of 638 hospitalizations due to respiratory diseases among children aged less than 10 years were evaluated during this period. The mean daily frequency of hospitalization was 1.75 cases (standard deviation, SD = 1.86), with a range from zero to 10 cases per day. In relation to the pollutants, the daily averages were 13.32  $\mu\text{g}/\text{m}^3$  (SD = 6.38) for the fine fraction and 22.45  $\mu\text{g}/\text{m}^3$  (SD = 13.25) for the coarse fraction ( $PM_{10-2.5}$ ). These values were significantly different ( $P < 0.01$ ). A high proportion of  $PM_{10-2.5}$  (62%) was found in the composition of  $PM_{10}$ . These data are shown in Table 1.

The period with the highest number of hospitalizations was from March to August. There were 59-113 hospitalizations per month during this period, representing 77% of all cases in the year 2015. This period coincides with the months during which sugarcane straw is burned and with the months when the weather is cooler.

Pearson correlation tests on the selected variables showed that the hospitalizations were positively and significantly correlated ( $P < 0.05$ ) with the  $PM_{2.5}$  and  $PM_{10-2.5}$  concentrations. Regarding the

mean temperature, hospitalizations showed significant negative correlations ( $P < 0.01$ ), thus demonstrating that low temperatures may be associated with hospitalizations (Table 2).

The regression coefficients and the respective standard errors for the concentrations of  $PM_{10-2.5}$  and  $PM_{2.5}$  at each lag time, with adjustments for mean temperature, relative humidity, short-term exposure (days of the week) and long-duration seasonality of exposure (annual) are shown in Table 3.

The significant relative risks of hospitalizations due to  $PM_{10-2.5}$  exposure were  $RR = 1.012$  (95% confidence interval, CI: 1.004-1.020) at lag 0 and  $RR = 1.011$  (95% CI: 1.003-1.019) at lag 6 (Figure 1).

**Table 1.** Descriptive analysis on the daily averages, minimum and maximum values and standard deviations of the study variables and the respective percentage values for pollutants. Piracicaba (SP), 2015

Variables	Mean (SD)	% <sup>(*)</sup>	Minimum-maximum	%
$PM_{2.5}$ ( $\mu\text{g}/\text{m}^3$ )	13.3 (6.4)	38.1 (7.1)	3-41	20.7-57.9*
$PM_{10-2.5}$ ( $\mu\text{g}/\text{m}^3$ )	22.5 (13.3)	61.9 (7.1)	5-85	42.1-79.3
Mean temperature ( $^{\circ}\text{C}$ )	23.2 (3.2)	-	14.8-31.2	-
Relative humidity (%)	48.3 (14.6)	-	13-88	-
Hospital admissions	1.8 (1.9)	-	0-10	-

SD = standard deviation.

\*in accordance with  $PM_{10}$  concentration.

**Table 2.** Pearson correlations for pollutants, mean temperature (MT), air relative humidity (RH) and hospitalizations (HA). Piracicaba (SP), 2015

	$PM_{2.5}$	$PM_{10-2.5}$	MT	RH	HA
$PM_{2.5}$	1	0.84**	0.11*	-0.61**	0.13*
$PM_{10-2.5}$		1	0.06	-0.64**	0.18*
MT			1	-0.28**	0.30**
RH				1	-0.01
HA					1

\* $P < 0.05$ ; \*\* $P < 0.01$ .

**Table 3.** Poisson regression coefficients and standard errors (SE; in parentheses) for the fine and coarse fractions according to the lag time. Piracicaba (SP), 2015

Lag	Coarse fraction (SE)	Fine fraction (SE)
0	0.01158 (0.00402) <sup>#</sup>	0.01083 (0.00785)
1	0.00425 (0.00420)	0.00577 (0.00825)
2	0.00245 (0.00446)	-0.00169 (0.00864)
3	0.00586 (0.00449)	0.01185 (0.00854)
4	0.00402 (0.00423)	0.00986 (0.00860)
5	0.00136 (0.00415)	0.00429 (0.00846)
6	<b>0.01107 (0.00401)<sup>#</sup></b>	0.01265 (0.00814)
7	0.00373 (0.00411)	-0.01270 (0.00841)

<sup>#</sup> $P < 0.05$ . SE = standard error.

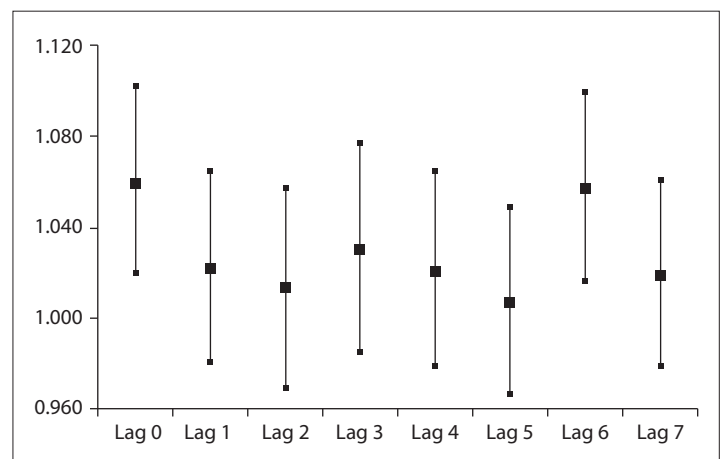
There was no significant association between exposure to the fine fraction and admissions, at any lag. Moreover, at lags 0 and 6, there was also no association between exposure to  $PM_{10}$  and admissions (data not shown). An increase of  $5 \mu\text{g}/\text{m}^3$  in the coarse-fraction concentration implied increases in the relative risk of hospitalizations of 4.8% and 4.6% for lag 0 and lag 6, respectively.

A reduction of  $5 \mu\text{g}/\text{m}^3$  in the coarse-fraction concentration would lead to a decrease of 73 hospitalizations, with a reduction in costs of around R\$ 52,000 over the period analyzed, considering R\$ 710.61 to be the mean cost of each hospitalization for the public healthcare system.

## DISCUSSION

The results from this study, which to the best of our knowledge was the first of its kind to be conducted in Brazil, showed that exposure to the coarse fraction of particulate matter was associated with hospitalizations due to respiratory diseases among children up to 10 years of age, both among hospitalizations on the same day as exposure (lag 0) and among hospitalizations six days after exposure (lag 6). The proportions between  $PM_{2.5}$  and  $PM_{10}$  found in the present study were of the order of approximately 38%, which differed from what has been reported in the literature (between 50 and 70%).<sup>16</sup>

There is evidence showing that short-term exposure to  $PM_{10}$  and long-term exposure to  $PM_{2.5}$  have effects involving increased mortality due to respiratory diseases. This demonstrates that the presence of both classes of particulate matter constitutes risk factors, even though greater emphasis has been placed on  $PM_{2.5}$  in the worldwide literature and presence of  $PM_{2.5}$  is considered to be more incisive in relation to emergence of respiratory diseases. It has been estimated that all-cause mortality (i.e. not only respiratory mortality) increases by 0.2-0.6% in response to an increase



**Figure 1.** Increased relative risks (RR) and corresponding 95% confidence intervals for all time lags, after an increase of  $5 \mu\text{g}/\text{m}^3$  in the concentration of  $PM_{10-2.5}$ , Piracicaba, SP, 2015.

of  $10 \mu\text{g}/\text{m}^3$  of  $\text{PM}_{10}$ .<sup>17</sup> In Brazil, the maximum concentrations of particulate matter ( $\text{PM}_{10}$ ) in six metropolitan areas of the country were above the limits established by the World Health Organization (WHO) in all years from 1995 to 2012, although these levels were within the limits established by Brazilian governmental agencies.<sup>18</sup>

Although the health implications of exposure to the coarse fraction ( $\text{PM}_{10-2.5}$ ) remain poorly explored and known, there seems to be an association between short-term exposure to this fraction and increased respiratory morbidity, especially as shown in daily averages in a meta-analysis performed by Adar et al.<sup>2</sup>

On the other hand, in a review article covering the period from 1995 to 2015, Froes Asmus et al.<sup>18</sup> showed that 17 ecological time series studies carried out in medium-sized and large Brazilian municipalities have been published and that all of them correlated increased numbers of hospital admissions due to respiratory diseases among children with increased concentrations of atmospheric pollutants, but that in none of these articles was exposure to the coarse fraction of particulate matter considered. This shows the importance of the results presented in our study.

Cesar et al.,<sup>3</sup> in Piracicaba (SP), used pollutant concentrations that were estimated through mathematical modeling (rather than from measurements) for the years 2011-2012. They observed that an increase in  $\text{PM}_{2.5}$  of  $10 \mu\text{g}/\text{m}^3$  implied an increase in the relative risk of respiratory morbidity among children aged zero to 10 years, between August 1, 2011, and July 31, 2012, of between 7.9% (lag 1) and 8.6% (lag 3). The mean concentration of  $\text{PM}_{2.5}$  was estimated at  $28.6 \mu\text{g}/\text{m}^3$  and the diseases studied were pneumonia and asthma.

In the present study, the data on the pollutants in the same city did not show any association between  $\text{PM}_{2.5}$  and hospitalizations due to respiratory diseases among children. Comparing our 2015 data with the 2011-2012 data from Cesar et al.,<sup>3</sup> we observed that our mean  $\text{PM}_{2.5}$  value ( $13.3 \mu\text{g}/\text{m}^3$ ) was approximately 50% of the mean  $\text{PM}_{2.5}$  value in their study. We may speculate that the lack of association in our study may have been due to this lower  $\text{PM}_{2.5}$  value in 2015, compared with 2011-2012. However, when the possible association of the role of exposure to the coarse fraction in hospitalizations due to some respiratory diseases was studied, associations were found at lags 0 and 6 with relative risks of approximately  $\text{RR} = 1.012$ . Although these isolated associations at lags 0 and 6 may have been due to chance, the effects of exposure to air pollutants usually occur around the fourth or fifth day. Nonetheless, the possibility that this effect might occur on the same day as the exposure cannot be ruled out.

Research on the effects of burning biomass have shown that this leads to impairment of respiratory functions especially among younger children.<sup>19-21</sup> In the city of Araraquara (SP), Souza and Nascimento<sup>22</sup> showed that an increase of  $10.0 \mu\text{g}/\text{m}^3$  in the concentration of  $\text{PM}_{10}$  led to increases in the relative risk of

hospitalizations among children up to 10 years of age of 15.0% at lag 0 and 7.0% at lag 1. These values were higher than what was obtained in the present study through analysis on the coarse fraction. The previous study used data from an earlier period (2010 to 2012) before the implementation of state laws to control the burning of sugarcane straw, which suggests that these laws have had a positive impact over recent years.

Souza et al.<sup>23</sup> conducted a study in Vitoria (ES) on daily hospital admissions of children under six years of age according to data on daily concentrations of air pollutants, including  $\text{PM}_{10}$ , that were collected in automatic monitoring stations. They showed that an increase of  $10 \mu\text{g}/\text{m}^3$  (interquartile range) in the levels of this pollutant resulted in a 3.0% increase in the relative risk of hospitalization.

Other differences between these two fractions relate to the longer half-life of the fine fraction (of the order of days to weeks), in contrast to the half-life of the coarse fraction (of the order of a few hours), and the greater distance that the fine fraction can reach, in comparison with the coarse fraction.<sup>24</sup>

Separate analysis on the fine and coarse fractions was justified in a study carried out in São José dos Campos (SP) where the compositions of these fractions were different. Ion concentrations differed, with higher levels of  $\text{SO}_4^{2-}$ ,  $\text{NH}_4^+$  and  $\text{K}^+$  in the fine fraction and higher levels of  $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{Na}^+$  and  $\text{Ca}^{2+}$  in the coarse fraction.<sup>25</sup>

It seems that there is greater production of hydroxyl radicals, increased production of cytokines by macrophages and easier stimulation of pulmonary macrophages to produce inflammatory mediators when there is exposure to the coarse fraction, in comparison with the fine fraction. Thus, this constitutes a difference in the mechanism of action between these two fractions.<sup>10</sup>

One limitation of this study may come from its exclusion of hospitalizations that were not within the National Health System (Sistema Único de Saúde, SUS). However, the present study is likely to have been representative of the Brazilian population because the majority of the population makes use of this service. Another limitation may relate to respiratory morbidities such as pneumonia, asthma and bronchitis among children, which may have been treated on an outpatient basis, without resulting in patient hospitalization, and thus such patients will not have been included in this study. In addition, cases of underreporting of respiratory diseases may also have occurred through errors in making diagnoses or in selecting the disease coding within the International Classification of Diseases (ICD), thus contributing towards some imprecise accounting of cases of morbidity. Despite the above, the DATASUS portal is an official source of the Brazilian Ministry of Health and the data available are accepted for use in epidemiological studies. Another possible limitation of this study is the monitoring of air pollutants during the study, since the daily concentrations of the pollutants ( $\text{PM}_{2.5}$  and  $\text{PM}_{10}$ ) obtained from CETESB stations were considered to be homogeneous for the whole municipality,

without evaluating the individual exposures to the pollutants analyzed here, and these were used to calculate the coarse fraction of the particulate material. In addition, the PM<sub>10-2.5</sub> data were not obtained directly, but were obtained from two quantified values, i.e. PM<sub>10</sub> and PM<sub>2.5</sub>, which may have contained errors.

## CONCLUSION

The results showed the effects of the coarse fraction of particulate matter on hospitalizations due to respiratory diseases among children, on the day of exposure and subsequently, up to six days afterwards. Another important finding from this study was that the concentration of the coarse fraction was high in relation to the fine particulate material, thus differing from what has been reported in the literature. In addition, the differences in these fractions that were observed regarding the sources where they originate and their compositions, half-lives, distances traveled and properties suggest that these fractions should be analyzed separately.

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# What do Cochrane systematic reviews say about new practices on integrative medicine?

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## ABSTRACT

**BACKGROUND:** This study identified and summarized all Cochrane systematic reviews (SRs) on the effects of ten integrative practices that were recently added to the Brazilian public healthcare system (SUS).

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

**METHODS:** Review of Cochrane SRs on the following interventions were identified, summarized and critically assessed: apitherapy, aromatherapy, bioenergetics, family constellation, flower therapy, chromotherapy, geotherapy, hypnotherapy, hand imposition or ozone therapy.

**RESULTS:** We included a total of 16 SRs: 4 on apitherapy, 4 on aromatherapy, 6 on hypnotherapy and 2 on ozone therapy. No Cochrane SR was found regarding bioenergetics, family constellation, chromotherapy, clay therapy, flower therapy or hand imposition. The only high-quality evidence was in relation to the potential benefit of apitherapy, specifically regarding some benefits from honey dressings for partial healing of burn wounds, for reduction of coughing among children with acute coughs and for preventing allergic reactions to insect stings.

**CONCLUSION:** Except for some specific uses of apitherapy (honey for burn wounds and for acute coughs and bee venom for allergic reactions to insect stings), the use of ten integrative practices that have recently been incorporated into SUS does not seem to be supported by evidence from Cochrane SRs.

## INTRODUCTION

On March 2018, the Brazilian Ministry of Health announced an expansion of its policies for integrative practices for healthcare within the Brazilian public healthcare system (Sistema Único de Saúde, SUS). Thus, ten new types of integrative practices now form part of the list of procedures available through SUS: apitherapy, aromatherapy, bioenergetics, family constellation, chromotherapy, clay therapy, hypnotherapy, hand imposition, ozone therapy and flower therapy.<sup>1</sup>

The term “integrative practice” commonly refers to incorporation of complementary approaches into a healthcare system.<sup>2</sup> It is important to differentiate between the concepts of “alternative” and “complementary” practices. When a non-mainstream practice is used together with conventional medicine, it is considered to be “complementary.” Conversely, when a non-mainstream practice is used in place of conventional medicine, it is considered to be “alternative.” Purely alternative approaches are seen less frequently, given that most people using non-mainstream approaches do so alongside conventional approaches.<sup>2</sup>

Most complementary healthcare practices can be classified as use of natural products or as use of mind and body practices. They may include use of probiotics, dietary supplements, yoga, chiropractic and osteopathic manipulation, meditation, massage therapy, acupuncture, healing touch, hypnotherapy, etc.<sup>2</sup>

Use of integrative practices may be justified for patients with chronic non-transmissible conditions whose clinical manifestations remain resistant or unresponsive to conventional treatments. However, their effectiveness and safety, and subsequently their cost-effectiveness and

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#### KEY WORDS:

Review [publication type].  
Public health administration.  
Evidence-based medicine.  
Integrative medicine.  
Health policy.

budgetary impact, need to be evaluated in order to guide their incorporation into public or private healthcare systems.

In this review, we identified and summarized all the Cochrane systematic reviews on the benefits and harm from use of ten integrative approaches that have recently been made available for users of SUS.

## OBJECTIVE

To summarize the evidence from Cochrane systematic reviews focusing on ten integrative practices for preventive or therapeutic purposes, for any disease or condition.

## METHODS

### Design

Review of Cochrane systematic reviews.

### Setting

Discipline of Evidence-Based Medicine of Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), and Cochrane Brazil.

### Criteria for including reviews

#### *Types of studies*

We considered the latest version of full Cochrane systematic reviews (SR). We excluded any protocol or any SR marked as “withdrawn” in the Cochrane Database of Systematic Reviews (CDSR).

#### *Types of participants*

We considered any healthy participant who received integrative practices for preventive purposes and any participant presenting any condition of illness who received integrative practices for therapeutic purposes.

#### *Types of interventions*

We included the integrative practices listed below that were used for preventive or therapeutic purposes and compared their use with no intervention or use of placebo or any other pharmacological or non-pharmacological intervention that was considered to represent a conventional, alternative or complementary approach. The integrative practices considered in this review are the same that are now provided in the Brazilian public health system, and comprised: apitherapy, aromatherapy, bioenergetics, family constellation, chromotherapy, clay therapy, hypnotherapy, hand imposition, ozone therapy and floral therapy. We only considered reviews that exclusively focused on one of these integrative interventions, rather than those addressing multiple interventions (called “umbrella” reviews).

#### *Type of outcomes*

We considered any clinical, social, laboratory or economic outcomes, as evaluated in the systematic reviews that were included.

### Search for reviews

We carried out a sensitive systematic search in the Cochrane Database of Systematic Reviews (via Wiley) on March 14, 2018. The search strategy is presented in **Table 1**.

Additionally, we conducted a manual search among titles listed on the web page “Cochrane Reviews and Protocols related to Complementary Medicine”, which is available from the Cochrane Complementary Medicine website: <http://cam.cochrane.org/cochrane-reviews-and-protocols-related-complementary-medicine>.

### Selection of systematic reviews

Two researchers (RLP and COC) independently screened and evaluated all records retrieved through the systematic search, to confirm their eligibility in accordance with the inclusion criteria. Any disagreements were resolved by consulting a third author (RR or DVP).

### Presentation of the results

We presented a summary of the reviews included, through a narrative approach (qualitative synthesis). The key points considered were the respective PICO (population, intervention, comparator and outcomes), methods for SR and meta-analyses, quality of primary studies included, quality of the body of the evidence for each outcome, and applicability. When multiple interventions were addressed by a single SR, we considered only those relevant for the present study.

## RESULTS

### Search results

The initial search retrieved 189 reviews and 13 protocols. After eliminating the protocols and assessing the full texts of the reviews, we excluded 173 reviews that did not fulfill our inclusion criteria. Thus, 16 Cochrane systematic reviews<sup>3-18</sup> were included and summarized, as follows.

### Results from systematic reviews

The 16 systematic reviews included related to four integrative practices: apitherapy (four SRs), aromatherapy (four SRs), hypnotherapy (six SRs) and ozone therapy (two SRs). In relation to the other six integrative practices (bioenergetics, family constellation, chromotherapy, clay therapy, hand imposition and flower therapy), no SR was retrieved through the search strategy and, therefore, no conclusion can be presented regarding their efficacy or safety.

The main findings from the SRs included and the quality of the evidence (based on the GRADE approach) are presented in **Table 2**. A brief summary of each SR is presented below.

#### 1. Apitherapy

Apitherapy refers to the use of byproducts from bees (honey, propolis or apitoxins) to promote health or as a treatment option for diseases.<sup>19</sup> It is a broad term, including different practices ranging from topical use of honey as a wound treatment to systemic use of processed apitoxins for immunomodulation.

##### 1.1 Honey as a topical treatment for wounds

This review<sup>3</sup> assessed the effects of honey, compared with alternative wound dressings and topical treatments, on the healing of acute and/or chronic wounds. It included 26 randomized clinical trials (RCTs, n = 3,011 participants). The RCTs included evaluated the effects of honey on:

- minor acute wounds (3 RCTs);
- burns (11 RCTs);
- different chronic wounds including venous leg ulcers (10 RCTs);
- diabetic foot ulcers (2 RCTs);
- infected postoperative wounds, pressure injuries, cutaneous leishmaniasis and Fournier’s gangrene (1 RCT each); and

**Table 1.** Search strategy

#1 MeSH descriptor: [Apitherapy] explode all trees
#2 MeSH descriptor: [Aromatherapy] explode all trees
#3 MeSH descriptor: [Color Therapy] explode all trees
#4 MeSH descriptor: [Therapeutic Touch] explode all trees
#5 MeSH descriptor: [Flower Essences] explode all trees
#6 (Apitherapy) OR (Apitoxins) OR (Apipuncture) OR (Bee Venom Therapy) OR (Bee Venom) OR (Honey) OR (Propolis) OR (Aromatherapy) OR (Bioenergetic) OR (Bioenergetic Therapy) OR (Bioenergetic Analysis) OR (Bioenergetic Psychotherapy) OR (Family Constellation) OR (Family Constellation Therapy) OR (Therapy, Color) OR (Chromatotherapy) OR (Chromotherapy) OR (Colour Light Therapy) OR (Geotherapy) OR (Hypnotherapy) OR (Hypnosis) OR (Healing Touch) OR (Hand Imposition) OR (Energy Channel) OR (Therapeutic Touch) OR (Energy Heal) OR (Laying-on-of-Hands) OR (Touch, Therapeutic) OR (Ozone) OR (Ozone Therapy) OR (Flower Essences) OR (Essences, Flower) OR (Bach Flower Remedies) OR (Flower Remedies, Bach) OR (Remedies, Bach Flower) OR (Bach Flowers) OR (Flowers, Bach) OR (Bach Flower Essences) OR (Essences, Bach Flower) OR (Flower Essences, Bach) OR (Flowering Top) OR (Top, Flowering) OR (Tops, Flowering) OR (Magnoliopsida) OR (Flowering Plants) OR (Flowering Plant) OR (Plant, Flowering) OR (Plants, Flowering) OR (Rosaceae) OR (Quince, Flowering) OR (Flowering Quinces) OR (Flowering Quinces) OR (Quinces, Flowering) OR (Passiflora) OR (Passion Flower) OR (Flower, Passion) OR (Flowers, Passion) OR (Passion Flowers) OR (Platycodon) OR (Balloon Flower) OR (Balloon) OR (Flower, Balloon) OR (Flowers, Balloon) OR (Fraxinus) OR (Flowering Ash) OR (Ash, Flowering) OR (Ashes, Flowering) OR (Flowering Ashes) OR (Inflorescence) OR (Flower Head) OR (Flower Heads) OR (Head, Flower) OR (Heads, Flower) OR (Florigen) OR (Flowering Hormone) OR (Hormone, Flowering) OR (Integrative)
#7 #1 or #2 or #3 or #4 or #5 or #6
Filters: in Cochrane Reviews; in Title, Abstract, Keywords

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

Integrative practice	Population and aim	Comparison	Benefits and harms	Evidence quality (GRADE approach)*
Honey (apitherapy) <sup>3</sup>	People with acute and/or chronic wounds	Conventional dressings for treatment of burns	• Honey dressings heal partial thickness burns more quickly than conventional dressings	High
			• No difference in overall risk of healing within six weeks for honey, compared with silver sulfadiazine	High
			• Burns treated with honey heal more quickly than those treated with silver sulfadiazine	Very low
			• Burns treated with honey presented lower risk of adverse events than the silver sulfadiazine group	High
Honey (apitherapy) <sup>4</sup>	Acute cough in children	Dextromethorphan, diphenhydramine, no treatment and placebo	• Use of honey was associated with reduced frequency of coughing, compared with the no treatment group	Moderate
			• Use of honey was associated with reduced frequency of coughing, compared with placebo	High
			• There was no difference between use of honey and use of dextromethorphan	Moderate
			• Use of honey was associated with reduced frequency of coughing, compared with diphenhydramine	Low quality
Venom immunotherapy (apitherapy) <sup>5</sup>	Preventing allergic reactions to insect stings	No intervention	• Use of venom immunotherapy versus no intervention reduced the risk of any systematic reaction to an insect sting	High
			• Reduction in the risk of large local reaction favoring venom immunotherapy	Moderate
			• The relative risk of any systematic reaction to treatment was higher with venom immunotherapy	Moderate
Aromatherapy <sup>7</sup>	Postoperative nausea and vomiting	Placebo, peppermint aromatherapy and isopropyl alcohol aromatherapy	• Aromatherapy reduced the use of rescue antiemetic medication, compared with placebo	Low
			• No difference between aromatherapy and placebo regarding: a) Severity of nausea b) Duration of nausea	Low Very low
			• No difference between peppermint aromatherapy and placebo regarding severity of nausea at five minutes	Low
			• Isopropyl alcohol aromatherapy showed benefits in relation to placebo for the following outcomes: a) time (in minutes) to 50% reduction of nausea score b) proportion of patients requiring antiemetics	Moderate Moderate
Aromatherapy <sup>8</sup>	Dementia	Placebo aromatherapy	This review included two RCTs with divergent results. No meta-analysis was performed because of heterogeneity and lack of data	Not assessed
Aromatherapy <sup>10</sup>	Pain management in labor	Standard care	No difference between groups regarding: a) assisted vaginal delivery risk b) cesarean section risk c) risk of neonatal intensive care admission	Not assessed
Hypnosis (hypnotherapy) <sup>13</sup>	Pain management during labor and childbirth	Placebo, no treatment or any analgesic drug or technique	• Use of pharmacological pain relief or anesthesia was lower in the group that received self-hypnosis or hypnotherapy, compared with standard care	Very low
			• No difference was found between the groups regarding: a) satisfaction with pain relief b) spontaneous vaginal birth	Low Low
Hypnosis (hypnotherapy) <sup>15</sup>	Schizophrenia	Any treatment or standard therapy	• No difference was found between hypnosis and standard care in relation to the brief psychiatric rating scale	Not assessed
Hypnosis (hypnotherapy) <sup>16</sup>	Smoking cessation	No intervention and other intervention strategies	• Benefit in hypnotherapy group regarding the probability of smoking cessation at 12 months, compared with no treatment • Compared with psychological treatments, hypnotherapy alone did not improve smoking cessation at six months	Not assessed
Ozone therapy <sup>17</sup>	Foot ulcers in people with diabetes	Antibiotic treatment or standard care	Compared with standard care, the ozone therapy group showed no difference regarding: • Ulcer area • Number of ulcers healed • Amputation rate • Adverse events	Not assessed

In this table, we only presented the results of systematic reviews that included studies that provided useful data. Thus, systematic reviews with no studies or with studies not containing any usable data were not included in this table.

\*GRADE (Grading of Recommendations Assessment, Development and Evaluation) has the aim of assessing the quality of the body of evidence. The evidence regarding a given outcome is assessed as having high quality (very high confidence in the results, i.e. the estimated effect is close to the true effect); moderate quality (it is very likely that the estimated effect is close to the real effect, but there is a possibility that it is not); low quality (the confidence in the effect estimate is limited); or very low quality (the true effect is likely to be substantially different from the estimate effect).

- mixed populations of patients with acute and chronic wounds (2 RCTs).

The main findings were:

- honey dressings heal partial-thickness burns more quickly than conventional dressings (weighted mean difference [WMD] -4.68 days; 95% confidence interval [95% CI] -5.09 to -4.28; two RCTs; 992 participants; high quality of evidence).
- no difference in overall probability of healing within six weeks for honey, compared with silver sulfadiazine (relative risk [RR] 1.00; 95% CI 0.98 to 1.02; six RCTs; 462 participants; high quality of evidence).
- burns treated with honey heal more quickly than those treated with silver sulfadiazine (WMD -5.12 days; 95% CI -9.51 to -0.73; four RCTs; 332 participants; very low quality of evidence).
- burns treated with honey presented lower risk of adverse events than the silver sulfadiazine group (RR 0.29; 95% CI 0.20 to 0.42; six RCTs; 412 participants; high quality of evidence).

All other evidence was sparse, and its quality was downgraded because of risk of bias and imprecision. There was high diversity regarding participant inclusions and comparators within the RCTs included. The high-quality evidence available from comparison of honey versus silver sulfadiazine needs to be interpreted with caution, since this was a head-to-head comparison and no inactive group was considered. Until further studies with strong methodological quality are available, no robust conclusions for practice can be reached regarding other interventions or regarding wounds other than burns. For further details and to access all analyses, refer to the original abstract, available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005083.pub4/full>.

### 1.2. Honey for treating acute coughing in children

This review<sup>4</sup> had the aim of evaluating the effects of honey on acute coughing in children. Three RCTs were included, comparing honey with dextromethorphan, diphenhydramine, no treatment and placebo.

All the RCTs provided data for the primary outcome of symptomatic relief of frequency of coughing. A seven-point Likert scale was used (the lower the score was, the less severe the cough symptom under assessment was). The main results were:

- Use of honey was associated with reduced frequency of coughing, in comparison with the no treatment group (mean difference [MD] -1.05; 95% CI -1.48 to -0.62; two RCTs; 154 participants; moderate quality of evidence).
- Use of honey was associated with reduced frequency of coughing, in comparison with placebo (MD -1.85; 95% CI -3.36 to -0.33; one RCT; 300 participants; high quality of evidence).

- There was no difference between use of honey and use of dextromethorphan (MD -0.07; 95% CI -1.07 to 0.94; two RCTs; 149 participants; moderate quality of evidence).
- Use of honey was associated with reduced frequency of coughing in comparison with diphenhydramine (MD -0.57; 95% CI -0.90 to -0.24; one RCT; 80 participants; low quality of evidence).

Although some results indicate that use of honey may be associated with better results than those obtained through no treatment, placebo or diphenhydramine, caution should be used until solid recommendations for practice can be issued. All the available evidence was based on small RCTs, and the follow-up of some RCTs was only for one night after the intervention. It needs to be borne in mind also that the primary outcome was based on a scale: the minimum clinically relevant difference needs to be investigated and considered when recommending honey for symptomatic relief of coughing. Although some RCTs presented data regarding adverse events, no significant difference between the groups was reported. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD007094.pub4/full>.

### 1.3. Venom immunotherapy for preventing allergic reactions to insect stings

This review<sup>5</sup> evaluated the effects of venom immunotherapy (VIT) for preventing allergic reactions to insect stings. Six RCTs and one quasi-randomized controlled trial (n = 392 participants) were included. Use of VIT against no intervention reduced the risk of any systematic reaction to an insect sting (RR 0.10; 95% CI 0.03 to 0.28; seven RCTs; 206 participants; high quality of evidence). There was also a reduction in the risk of large local reaction, favoring VIT (RR 0.41; 95% CI 0.24 to 0.69; five RCTs; 112 participants; moderate quality of evidence). Regarding safety outcomes, systematic reaction to treatment was evaluated. The relative risk was higher in the VIT group (RR 8.16; 95% CI 1.53 to 43.46; six RCTs; 285 participants; moderate quality of evidence).

The authors of this review concluded that there was evidence supporting the use of VIT for preventing allergic reactions to insect stings. However, they considered that the low number of events in the groups would need to be taken into account and that further studies would be needed to reduce the imprecision in some results. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD008838.pub2/full>.

### 1.4 Honey and lozenges for children with nonspecific coughs

This review<sup>6</sup> aimed to evaluate the effects of honey and lozenges among children with chronic nonspecific coughs. The authors of this review conducted their search in 2009 and their strategy

did not find any RCTs that fulfilled the inclusion criteria. Until further studies have been developed and this review has been updated, no solid conclusions for practice can be reached. For further information, refer to: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007523.pub2/full>.

## 2. Aromatherapy

Aromatherapy is any type of treatment that involves use of essential oils. These might be obtained from herbs, flowers or other plants.<sup>19</sup> The compounds can be administered topically or through inhalation or water immersion.

### 2.1 Aromatherapy for treatment of postoperative nausea and vomiting

This review<sup>7</sup> aimed to assess the efficacy and safety of aromatherapy for treatment of postoperative nausea and vomiting. Sixteen controlled trials were included (n = 1,036 participants). Compared with placebo, aromatherapy reduced the use of rescue antiemetic medication (RR 0.60; 95% CI 0.37 to 0.97; seven RCTs; 609 participants; low quality of evidence). No difference between the groups was found regarding the following outcomes:

- severity of nausea, assessed on a visual analogue scale at the end of treatment (SMD -0.22; 95% CI -0.63 to 0.18; six RCTs; 241 participants; low quality of evidence); and
- proportion of participants without nausea at the end of treatment (RR 3.25; 95% CI 0.31 to 34.33; four RCTs; 193 participants; very low quality of evidence).

A specific analysis comparing peppermint aromatherapy versus placebo found no difference in severity of nausea at five minutes (SMD -0.18; 95% CI -0.86 to 0.49; four RCTs; 115 participants; low quality of evidence). No data were pooled for other outcomes.

Comparison of isopropyl alcohol aromatherapy with placebo showed that this treatment provided benefits regarding the following outcomes:

- time (in minutes) to 50% reduction of nausea score (SMD -1.10 minutes; 95% CI -1.43 to -0.78; 3 RCTs; 176 participants; moderate quality of evidence); and
- proportion of patients requiring antiemetics (RR 0.67; 95% CI 0.46 to 0.98; four RCTs; 215 participants; moderate quality of evidence).

No difference was found between the groups regarding patient satisfaction (RR 1.12; 95% CI 0.62 to 2.03; two RCTs; 172 participants; very low quality of evidence).

The overall methodological quality of the studies was considered low by the review authors. The adverse events were poorly reported, and no data were pooled. They considered that further studies would be imperative for solid conclusions to be drawn for

practice. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD007598.pub3/full>.

### 2.2 Aromatherapy for dementia

This review<sup>8</sup> assessed the efficacy of aromatherapy for people with dementia. Seven RCTs were included (n = 428 participants). These compared the use of any fragrance from plants versus placebo aromatherapy. Overall, the studies included presented important uncertainties relating to methodological issues, low numbers of participants and lack of data reporting. The authors of this review retrieved individual participant data from one RCT that showed statistically significant differences favoring aromatherapy in the Cohen-Mansfield Agitation Inventory (CMAI) after four weeks of treatment (MD -11.1; 95% CI -19.9 to -2.2; one RCT; 71 participants) and in behavioral symptoms according to the Neuropsychiatric Inventory (MD -15.8; 95% CI -24.4 to -7.2; one RCT; 71 participants). These results were conflicting with the results from another RCT, in which there was no difference according to the Neuropsychiatric Inventory scale (MD 2.80; 95% CI -5.84 to 11.44; one RCT; 63 participants). There was no difference in adverse events between aromatherapy and placebo (RR 0.97; 95% CI 0.15 to 6.46; two RCTs; 124 participants; very low quality of evidence). The authors did not pool any other results because of the high diversity of the clinical and methodological aspects of the RCTs. Better designed and better reported RCTs are still needed in order to reduce the uncertainties and to make practical recommendations. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD003150.pub2/full>.

### 2.3 Massage plus aromatherapy for symptom relief in people with cancer

This review<sup>9</sup> assessed the effects of massage with or without aromatherapy on relief of symptoms in people with cancer. Only two small RCTs (n = 117 participants) were included, and these provided isolated analyses on the effects of aromatherapy effects. Considering the sample size and methodological and reporting limitations of both RCTs, the authors were unable to pool any data regarding pain relief, psychological symptoms or quality of life. Therefore, no solid conclusions can be reached regarding the addition of aromatherapy to massage for symptom relief in cancer patients. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009873.pub3/full>.

### 2.4 Aromatherapy for pain management in labor

This review<sup>10</sup> assessed the effects of aromatherapy for pain management in labor. Two RCTs (n = 535 participants) were

included. The aim was to compare aromatherapy with another form of aromatherapy or with placebo, no treatment or other complementary interventions. Only one RCT (n = 513) compared aromatherapy with standard care, but no reliable data regarding pain intensity was reported. There were no differences in the risks of assisted vaginal delivery (RR 1.04; 95% CI 0.48 to 2.28; one RCT; 513 participants), caesarian section (RR 0.98; 95% CI 0.49 to 1.94; one RCT; 513 participants) or neonatal intensive care admission (RR 0.08; 95% CI 0.00 to 1.42; one RCT; 513 participants). The data from the other RCT (n = 22 participants) compared two forms of aromatherapy and will not be presented here. Until further results are available, no conclusion can be drawn regarding aromatherapy for pain management in labor. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009215/full>.

### 3. Bioenergetics

Bioenergetic analysis is a specific form of body psychotherapy. The bioenergetic approach has the aim of functioning through verbalization, corporal education and respiration techniques.<sup>19</sup> Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

### 4. Chromotherapy

Chromotherapy or color therapy is a therapeutic technique that uses colors of the electromagnetic spectrum. The principle is that each color has an effect on the body and this may be converted into a therapeutic approach.<sup>19</sup> Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

### 5. Family constellation

Family constellation is a psychotherapeutic method that aims to help patients by identifying hidden and transgenerational patterns of behavior in the family structure. It has the aim of leading towards resolution of conflicts within the family unit and within the individual perspective.<sup>19</sup> Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

### 6. Flower therapy

Flower therapy is a therapeutic approach that uses flower-derived essences. There is a theory that the use of floral therapy might act on mental state and emotions.<sup>19</sup> Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

### 7. Geotherapy

Geotherapy is defined as therapeutic use of a mixture of clay minerals and water in the form of cataplasms or mud baths applied to the

skin.<sup>19</sup> It is empirically used in esthetics and in treating dermatological and rheumatological diseases. Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

## 8. Hypnotherapy

The term hypnotherapy refers to a group of techniques that uses hypnosis to treat health-related conditions. It assumes that through concentration and relaxation maneuvers, the patient may be able to change undesired conditions and behaviors.<sup>19</sup>

### 8.1 Hypnotherapy for treatment of irritable bowel syndrome

This review<sup>11</sup> assessed the effects of hypnotherapy on the management of irritable bowel syndrome, in comparison with no treatment, waiting list or another therapeutic intervention. Four RCTs (n = 147 patients) were included. Because of the small sample size, poor reporting of outcomes and lack of methodological quality, no solid conclusions could be drawn. No meta-analysis was performed because there was important heterogeneity between the RCTs included. This systematic review was performed in 2010 and no assessment of the overall quality of the evidence was performed. The risk-of-bias assessment also needs to be updated to the new Cochrane standards. Until further RCTs and an updated SR have been conducted, the uncertainty regarding the use of hypnotherapy for treating irritable bowel syndrome remains. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD005110.pub2>.

### 8.2 Hypnosis during pregnancy, childbirth and the postnatal period for preventing postnatal depression

This review<sup>12</sup> had the aim of evaluating the benefits and harm of hypnosis for preventing postnatal depression, in comparison with the regular antenatal, natal and postnatal care. The authors of this review aimed to assess the development of postnatal depression, using a validated scale, and other secondary outcomes, such as postnatal psychosis, anxiety disorders, maternal mortality, suicidal ideation and death by suicide. One RCT was included (n = 63 participants). However, the data provided for evaluation of the effect of hypnosis was insufficient and poorly reported. Thus, further RCTs are imperative for solid conclusions regarding this topic to be reached. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009062.pub2/abstract>.

### 8.3 Hypnosis for induction of labor

This review<sup>13</sup> aimed to evaluate the effects of hypnosis for induction of labor, compared with no intervention or any other interventions. The search was conducted in 2014 and no RCTs fulfilled

the inclusion criteria. No conclusions can be drawn until appropriate RCTs have been developed. For further details, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD010852.pub2/abstract>.

#### 8.4 Hypnosis for pain management during labor and childbirth

This review<sup>14</sup> evaluated the effects of hypnosis for pain management in childbirth and labor. Seven RCTs and quasi-controlled trials (n = 1,213 participants) were included. They compared the use of hypnosis during or before labor versus placebo, no treatment or use of any analgesic drug or technique (control groups). The use of pharmacological pain relief or anesthesia was lower in the group that received self-hypnosis or hypnotherapy, compared with standard care (RR 0.73; 95% CI 0.57 to 0.94; eight RCTs; 2,916 participants; very low quality of evidence). No difference was found between the groups regarding satisfaction with pain relief (RR 1.06; 95% CI 0.94 to 1.20; one RCT; 264 participants; low quality of evidence) or spontaneous vaginal birth (RR 1.12; 95% CI 0.96 to 1.32; six RCTs; 2,631 participants; low quality of evidence). The overall quality of these data was downgraded because of design limitations, high inconsistency and imprecision. The studies included in the pooled analysis were very heterogeneous, and this needs to be considered in interpreting these results. No solid conclusion can be drawn until further studies have been conducted. The authors performed many analyses and subgroup investigations. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009356.pub3/full>.

#### 8.5 Hypnosis for schizophrenia

This review<sup>15</sup> assessed the efficacy and safety of hypnosis for people with schizophrenia or schizophrenia-like illnesses, compared with any other treatment or standard therapy. Three RCTs were included (n = 149 participants). The main outcomes that the review aimed to investigate were: number of participants who dropped out before completion of the study; mental score, evaluated using the brief psychiatric rating scale (BPRS); movement disorders; and neurocognitive function.

Two RCTs evaluated hypnosis versus standard treatment. In both, none of the patients left the study early (within the first 12 weeks) in either group (risk difference [RD] 0.00; 95% CI -0.09 to 0.09; two RCTs; 70 participants). No difference was found between hypnosis and standard care regarding the BPRS scale (MD -3.63; 95% CI -12.05 to 4.79; one RCT; 60 participants). All other outcomes relating to hypnosis versus standard treatment were poorly reported. The authors also made head-to-head comparisons with music and relaxation techniques. Until further RCTs that are well designed and well reported have been conducted, no solid conclusions for practice can be drawn. For further details and to access all analyses,

refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD004160.pub3/full>.

#### 8.6 Hypnotherapy for smoking cessation

This review<sup>16</sup> evaluated the effects of hypnotherapy for smoking cessation, compared with no intervention and other intervention strategies. Eleven RCTs (n = 1,120 participants) that compared hypnotherapy with 18 different interventions were included.

Only one RCT (n = 20 participants) compared hypnotherapy with no treatment (a waiting list control), and this study found that there was a benefit for the hypnotherapy group regarding the probability of smoking cessation at 12 months (RR 19.00; 95% CI 1.18 to 305.88; one RCT; 20 participants). Compared with psychological treatments, hypnotherapy alone did not improve the probability of smoking cessation at six months (RR 0.93; 95% CI 0.47 to 1.82; two RCTs; 211 participants).

Despite the considerable number of RCTs included, they were highly heterogeneous regarding comparisons and methodological aspects, which prevented large quantitative synthesis. The risk of bias of each study also needed to be considered, and the overall quality of the evidence was not assessed in this SR. Until further RCTs have been conducted and this SR has been updated, no solid conclusions for practice can be reached. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD001008.pub2/full>.

### 9. Imposition of hands

Imposition of hands is, as defined in the Brazilian Ministry of Health's Glossary for Integrative and Complementary Practices in Healthcare, "a secular therapeutic practice that implies a meditative effort to transfer vital energy (such as Qi or prana, i.e. a universal vital energy that permeates the cosmos and constitutes all that exists) through the hands, in order to re-establish the equilibrium of the human energy field, thereby assisting in the health-disease process." It is believed that imposition of hands could be beneficial for decreasing the levels of pain, depression and anxiety.<sup>19</sup> Our search strategy did not retrieve any Cochrane systematic review addressing this intervention.

### 10. Ozone therapy

Ozone is a molecule composed of three oxygen atoms. It has an unstable structure that makes it a powerful oxidant that can be administered in precise therapeutic doses. Some authors have claimed that it has health benefits under a variety of conditions characterized by hypoxic and ischemic syndromes.<sup>20</sup>

#### 10.1 Ozone therapy for treating foot ulcers in people with diabetes

This review<sup>17</sup> assessed the efficacy and safety of ozone therapy for treating foot ulcers in patients with diabetes mellitus. Three RCTs

(n = 212 participants) were included. One RCT (n = 101) compared the effects of ozone versus antibiotic treatment and showed that there was greater reduction in ulcer area in patients treated with ozone therapy (MD -20.54 cm<sup>2</sup>; 95% CI -20.61 to -20.47; one RCT; 101 participants), along with shorter duration of hospitalization (MD -8.00 days; 95% CI -14.17 to -1.83; one RCT; 101 participants); but that this did not alter the number of ulcers healed over 20 days (RR 1.10; 95% CI 0.87 to 1.40; one RCT; 101 participants). No adverse events were reported in either group. Another two RCTs (111 participants) compared the effects of ozone plus the usual care (debridement, daily wound dressings and moisturization) versus the usual care. There were no differences in the following: ulcer area (MD -2.11 cm<sup>2</sup>; 95% CI -5.29 to 1.07; two RCTs; 111 participants), number of ulcers healed (RR 1.69; 95% CI 0.90 to 3.17; two RCTs; 111 participants), amputation rate (RR 2.73; 95% CI 0.12 to 64.42; two RCTs; 111 participants) and adverse events (RR 2.27; 95% CI 0.48 to 10.79; two RCTs; 111 participants). Considering the small sample size and the methodological flaws of the studies included, the authors could not draw any solid conclusions for practice. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD008474.pub2/full>.

### 10.2 Ozone therapy for treating dental caries

This review<sup>18</sup> assessed the efficacy and safety of ozone therapy for controlling the progression of dental caries. Three RCTs were included (n = 137 participants). The authors of this SR aimed to evaluate the progression of caries in unrestored cases, use of further conventional treatment, time to intervention, cost, patient satisfaction and adverse events. All three RCTs included in this review evaluated local outcomes that the authors did not consider to be suitable for data pooling, so they did not do this. They concluded that there was no reliable evidence to support the use of ozone for treating dental caries. For further details and to access all analyses, refer to the original abstract, available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD004153.pub2/full>.

## DISCUSSION

This overview of reviews included 16 systematic reviews (SRs) that assessed the use of 4 out of the 10 integrative practices that were recently added to the procedures available through the Brazilian public healthcare system (SUS). The specific topics found were apitherapy (four SRs), aromatherapy (four SRs), hypnotherapy (six SRs) and ozone therapy (two SRs). No Cochrane SRs was found regarding bioenergetics, family constellation, chromotherapy, geotherapy, flower therapy or hand imposition.

Overall, the Cochrane reviews included reported high-quality evidence regarding some outcomes from the use of apitherapy.

All other evidence that was reported ranged in quality from unknown to moderate.

Honey dressings seemed to have some benefit over conventional dressings for the time needed to achieve partial healing of burn wounds, although this could be considered to be a surrogate outcome (if total healing were taken to be the clinically relevant outcome instead). Use of honey also seemed to reduce the frequency of coughing among children with acute coughs. Additionally, use of bee venom therapy seemed to prevent systematic allergic reactions to insect stings.

This overview made it clear that there are uncertainties regarding the efficacy and safety of the ten integrative practices that have recently been added to the procedures available through the Brazilian public healthcare system. Cochrane SRs are considered by many people to be the gold standard for evaluation of interventions within healthcare. Despite our wide-ranging search in the Cochrane database and broad inclusion criteria, we found that there was a lack of SRs investigating many topics (SRs were only available in relation to four out of these ten topics).

The absence of SRs relating to these topics may be indirectly indicative of the lack of controlled experimental studies assessing integrative practices. All of these practices need to be considered in the same way as any other intervention. There may have benefits, no effect or harm after their use. Any intervention, including integrative practices, is subject to adverse events and the safety component needs to be assessed in any evaluation.

This review has some limitations. Our search was conducted in a single database, even though the Cochrane Library is recognized as the most important database of systematic reviews. The limited data available on each topic is a consequence of the small number of studies, and the low quality of the evidence relates to the small sample sizes and risk of bias of the RCTs. Another point that should be noted is the huge variety of techniques for each integrative and complementary health practice that were considered in the primary studies that were included in these systematic reviews, which led to difficulty in identifying the overall effect of each intervention.

Regarding practical implications, except for a single case (apitherapy, i.e. specifically use of honey for partial healing of wound burns and for treating acute coughs; and bee venom therapy for preventing allergic reactions to insect stings), the use of these ten integrative practices that were recently incorporated into SUS does not seem to be supported by adequate evidence found in Cochrane SRs. Thus, for many integrative practices, no randomized clinical trial was found. This does not mean that no benefit exists, but it does mean that huge uncertainties remain, regarding the benefits and harm associated with use of such interventions.

Hence, it appears that the incorporation of these ten integrative practices into SUS is in disagreement with Brazilian Federal law number 12,401 (of April 2011), which establishes that health technologies,

including medicines, orthoses, prostheses, diagnostic and therapeutic procedures and health care, can be incorporated into the public healthcare system (SUS) only when the National Commission for Incorporation of Technologies (CONITEC) finds scientific evidence of efficacy, accuracy, effectiveness and safety in relation to the drug, product or procedure under analysis that is accepted by the institution in charge of registration or authorization for use.<sup>21</sup>

Regarding the implications for research, this review found out that much remains to be done in relation to establishing what effects the IPs addressed here have for healthcare. RCTs with high methodological quality are recommended before any health intervention is brought into routine prescription and use. Subsequently, cost-effectiveness studies will need to be developed for the integrative practices that were proven to be effective and safe (as findings from RCTs). Economic studies analyzing these integrative practices in terms of their consequences for health and their economic burden are also worthwhile.

## CONCLUSION

This review identified 16 Cochrane systematic reviews that provided evidence, of a range of quality, in relation to ten new integrative practices that were recently incorporated into the Brazilian public healthcare system (SUS). Except for a few cases of apitherapy (honey dressings for partial healing of wound burns, honey to reduce coughing among children with acute coughs and bee venom to prevent allergic reactions to insect stings), none of the integrative practices addressed by the present review are supported by Cochrane SRs, because

- there is a lack of primary studies; or
- no Cochrane SRs exist (bioenergetics, chromotherapy, family constellation, flower therapy, geotherapy and imposition of hands); or
- the evidence found so far is insufficient for producing any sound conclusion. Evidence from additional sources regarding the effects of other integrative practices that have not been addressed by Cochrane SRs needs to be searched for.

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# Metastatic adenocarcinoma involving the right ventricle and pulmonary artery leading to right heart failure: case report

Adenocarcinoma metastático envolvendo o ventrículo direito e artéria pulmonar levando a insuficiência cardíaca direita: relato de caso

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## KEY WORDS:

Neoplasm metastasis.  
Adenocarcinoma.  
Echocardiography.  
Heart failure.  
Pulmonary artery.

## PALAVRAS-CHAVE:

Metástase neoplásica.  
Adenocarcinoma.  
Ecocardiografia.  
Insuficiência cardíaca.  
Artéria pulmonar.

## ABSTRACT

**CONTEXT:** Obstruction of the right ventricular outflow tract due to metastatic disease is rare. Clinical recognition of cardiac metastatic tumors is rare and continues to present a diagnostic and therapeutic challenge.

**CASE REPORT:** We present the case of a patient who had severe respiratory insufficiency and whose clinical examinations revealed a giant tumor mass extending from the right ventricle to the pulmonary artery. We discuss the diagnostic and therapeutic options.

**CONCLUSION:** In patients presenting with acute right heart failure, right ventricular masses should be kept in mind. Transthoracic echocardiography appears to be the most easily available, noninvasive, cost-effective and useful technique in making the differential diagnosis.

## RESUMO

**CONTEXTO:** A obstrução da via de saída do ventrículo direito devido a doença metastática é rara. O reconhecimento clínico de tumores cardíacos metastáticos é raro e continua a apresentar um desafio diagnóstico e terapêutico.

**RELATO DO CASO:** Apresentamos o caso de um paciente com insuficiência respiratória grave e cujos exames clínicos revelaram massa de tumor gigante, estendendo-se desde o ventrículo direito até a artéria pulmonar. Discutimos as opções diagnósticas e terapêuticas.

**CONCLUSÃO:** Em pacientes com insuficiência cardíaca direita aguda, massas do ventrículo direito devem ser mantidas em mente. Ecocardiografia transtorácica parece ser a técnica mais facilmente disponível, não invasiva, custo-efetiva e útil no diagnóstico diferencial.

## INTRODUCTION

Tumors involving the heart are more commonly metastatic than primary, and the prognosis for metastatic tumors in the heart is extremely poor. Involvement of the right heart is more common than that of the left heart and the clinical course is usually silent in most patients.<sup>1</sup> This report presents the case of a 67-year-old male patient with no previous diseases, in whom a metastatic right cardiac tumor invading the right ventricular outflow tract and the pulmonary artery was detected. We also discuss the diagnostic and therapeutic techniques.

## CASE REPORT

A 67-year-old male patient was admitted to the emergency department with a 15-day history of progressive fatigue, shortness of breath and respiratory insufficiency. The patient stated that he had not had any complaints until 15 days before admission, and no previous diseases had been documented. He reported having progressive shortness of breath, which first appeared during exercise 15 days earlier and had then even become apparent at rest. The patient reported having made intermittent use of paracetamol for headache for years. He had a history of smoking and intermittent alcohol use.

On admission, the patient's general condition was poor, with severe shortness of breath. He was orthopneic and was using accessory muscles while breathing. His blood pressure was 80/65 mmHg, and his pulse was 128/minute. His breathing sounds were rough but no rales or rhonchi were heard. Heart sounds were tachycardic, and there was a 2/6 systolic murmur heard in the tricuspid area. He had 1+ edema of both feet. A chest x-ray showed increased vascularization, a dilated pulmonary artery and a cardiothoracic index of > 1. An electrocardiogram revealed an incomplete right bundle branch block and a negative T wave in the V1-3 leads.

Laboratory tests conducted on venous blood sample showed that blood glucose was 124 mg/dl (normal range 74-100); urea, 90.2 mg/dl (normal range 0-50); creatinine, 1.6 mg/dl (normal range 0-1.2); sodium, 134 mg/dl (normal range 132-146); and potassium, 5.2 mg/dl (normal range 3.5-5.5). Liver function tests revealed elevated values: aspartate transaminase, 3418 U/l (normal range 0-50); alanine transaminase, 1204 U/l (normal range 0-50); alkaline phosphatase, 276 U/l (normal range 30-120); and lipase, 92 U/l (normal range 0-67). Total bilirubin and direct bilirubin levels were slightly elevated: 8.4 g/dl (normal range 6.6-8.3) and 0.24 mg/dl (normal range 0-0.2), respectively. The hemogram was unremarkable except for leukocytosis. The prothrombin time was 21.2 seconds and was slightly lengthened (normal range 10.4-14.6 seconds). Cardiac markers were also slightly elevated: troponin I, 0.45 ng/ml (normal range 0-0.001); and creatinine kinase-myocardial band, 6.4 ng/ml (normal range 0.6-6.3). An arterial blood gas test revealed pH of 7.49,  $sO_2$  of 87.9%,  $pO_2$  of 57.2 mmHg and  $pCO_2$  of 22.5 mmHg.

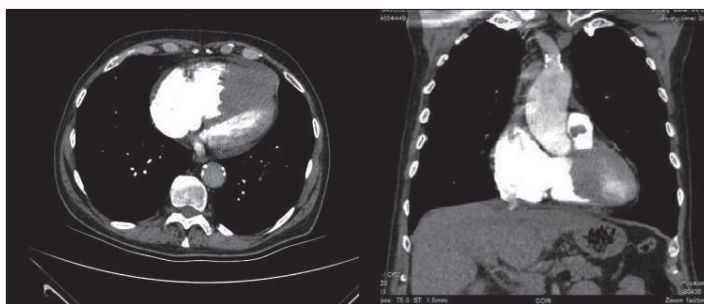
In the light of these data, the patient received an initial diagnosis of acute toxic hepatitis, taking into consideration the history

of pulmonary embolism and recent use of medication. A complete abdominal ultrasound examination revealed a slightly enlarged liver. A contrast computed tomography pulmonary angiogram was performed and did not show any thrombus in the major arteries or their branches. On the other hand, a filling defect from the right ventricle to the pulmonary artery, which was interpreted to represent a thrombus, was observed (Figure 1).

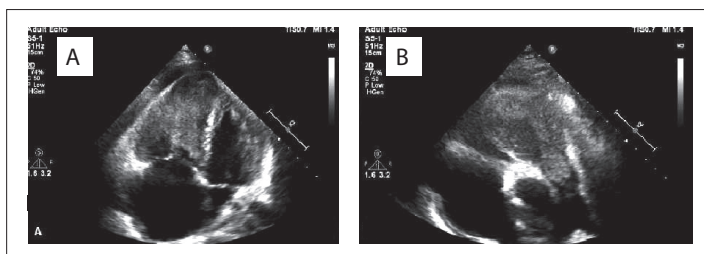
Therefore, transthoracic echocardiography was performed, revealing a considerably enlarged right ventricle and a flattened interventricular septum, which had shifted towards the left ventricle. A 6 cm x 5 cm mass, consistent with thrombus echogenicity, was detected inside the right ventricle. It extended to the pulmonary artery, with invasion of the pulmonary valve, giving rise to to-and-fro motion in each systole (Figure 2).

Right ventricular systolic function was considerably decreased (tricuspid annular plane systolic excursion, TAPSE: 1.6 cm). Left ventricular systolic function was slightly decreased. Severe tricuspid and mitral insufficiency was present. Pulmonary artery systolic pressure was elevated (60 mmHg).

Thus, the patient was referred for consultation in the department of cardiovascular surgery and was immediately scheduled for emergency surgery. During surgery, it was found that the mass was a tumor. The tumor had invaded the anterior wall of the right ventricle, interventricular septum and right ventricular outflow tract. The tumor was removed from the interventricular septum and the



**Figure 1.** Contrast computed tomography pulmonary angiogram showing a dilated right ventricle and a filling defect, both in the right ventricle and in the pulmonary artery.

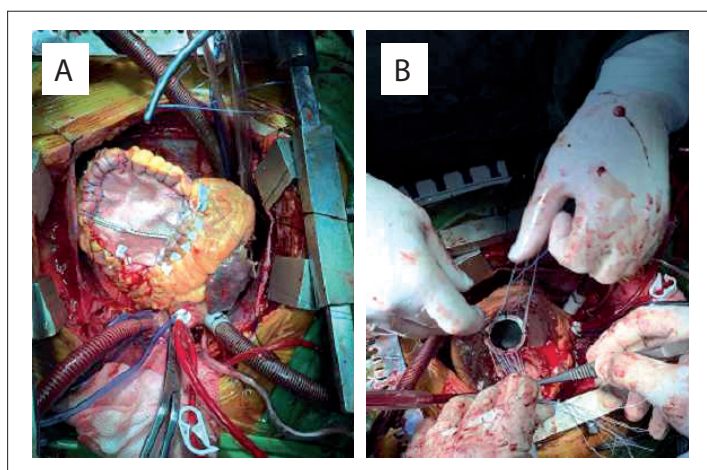


**Figure 2.** Echocardiogram showing the mass inside the right ventricle, which extended to the pulmonary artery and invaded the pulmonary valve, in apical four-chamber view (A) and parasternal short-axis view (B).

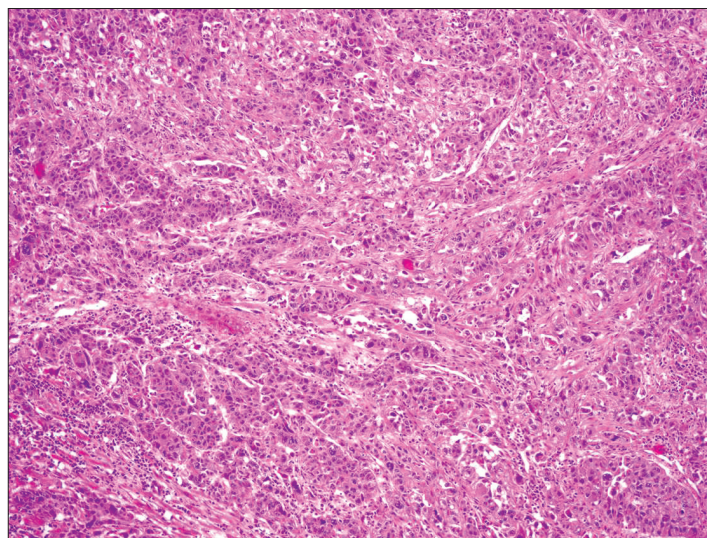
anterior wall of the right ventricle. The resulting ventricular septal defect was closed with a patch (**Figure 3a**) and the tricuspid valve was replaced (**Figure 3b**). Intraoperative transesophageal echocardiography revealed only moderate mitral insufficiency, and therefore mitral valve replacement was not considered.

The pathology report showed that the mass was a poorly differentiated metastatic adenocarcinoma, which had probably originated from the lungs. It exhibited partial neuroendocrine differentiation (**Figure 4**).

The patient's postoperative hemodynamic condition did not improve, despite inotropic support. He developed cardiopulmonary arrest on postoperative day 3 and died, despite resuscitation attempts.



**Figure 3.** Resection of tumor from the heart, with closure of the ventricular septal defect using a patch (A) and replacement of the tricuspid valve (B).



**Figure 4.** Adenocarcinoma infiltration to the myocardium. Tumor cells form coarse solid trabecular structures (100 x; hematoxylin and eosin).

## DISCUSSION

Tumors that are metastatic to the heart are rare. Cardiac involvement at autopsy has been described in 6% to 20% of patients with malignant neoplasms.<sup>2</sup> The lungs have been reported to be the most common primary origin of metastatic neoplasms, followed by nonsolid neoplasms such as lymphoma or leukemia and tumors of the liver and colon, respectively.<sup>3</sup> The epicardium is the most commonly involved site, followed by the myocardium and the endocardium.<sup>4</sup>

The systematized results from searching the literature through the main databases are presented in **Table 1**. The data in the literature show that diagnosing and treating tumors located in the right ventricular outflow tract is extremely challenging. The symptoms usually depend on the size and location of the tumor. The most common symptoms include shortness of breath, syncope and cyanosis.<sup>5</sup> Some patients may present with nonspecific symptoms and tumors are usually detected incidentally. Inability to measure blood pressure with the patient in the seated position is likely to indicate occlusion of the pulmonary artery by the tumor.<sup>5</sup> These tumors may reach huge sizes, thus resulting in occlusion of the right ventricular outflow tract and right ventricular volume overload and dilation, which is likely to result in severe right ventricular failure.<sup>6</sup> In addition, neoplasms may cause fatal clinical consequences including arrhythmia, acute heart failure and sudden death. Tumors may disintegrate into fragments, thus embolizing the pulmonary vascular bed. Accordingly, patients may present with clinical signs and symptoms of pulmonary embolism. Emergency surgery should be considered upon detection of right ventricular outflow tract obstruction.<sup>4</sup> Early diagnosis enables timely surgical treatment, thus increasing survival. In addition, the data in the literature indicate that postoperative adjuvant chemotherapy may be useful in patients with adenocarcinomas of gastrointestinal origin that are metastatic to the heart.<sup>7,8</sup>

In the case presented here, the patient presented with a 15-day history of progressive shortness of breath. He showed clear signs and symptoms of right ventricular failure. A diagnosis of pulmonary embolism was initially considered, but firstly contrast computed tomography and then transthoracic echocardiography revealed an intracardiac tumor. Upon detection of obliteration of the right ventricular outflow tract and invasion of the pulmonary

**Table 1.** Systematic search of the literature performed in April 2016

Database	Search strategies	Found	Used
MEDLINE (via PubMed)	(metastatic adenocarcinoma) and (heart)	1,388	4
LILACS (via Bireme)	(metastatic adenocarcinoma) and (heart) and (pulmonary)	0	0
Cochrane Library	(metastatic adenocarcinoma) and (heart) and (failure)	30	0

valve by the tumor, the patient was sent for emergency surgery. Despite successful excision of the mass, the patient's postoperative hemodynamic condition did not improve, even though inotropic support was provided, and he subsequently died.

Although the tumor was diagnosed pathologically, the origin of the tumor could not be identified. Pathologically, the tumor was likely to have originated from the lungs, gastrointestinal tract or pancreaticobiliary system. However, this could not be confirmed because the patient's family did not give permission for an autopsy.

## CONCLUSION

Right ventricular metastatic tumors are relatively rarer than other types. In patients presenting with shortness of breath with rapid progression and right heart failure, right ventricular obstruction should be kept in mind, along with other possible diagnoses. Transthoracic echocardiography appears to be the most easily available, noninvasive, cost-effective and useful technique in making the differential diagnosis.

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# Flexible bronchoscopy and mechanical ventilation in managing Mounier-Kuhn syndrome: a case report

Broncoscopia flexível e ventilação mecânica no tratamento da síndrome de Mounier-Kuhn: relato de caso

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## KEY WORDS:

Bronchoscopy.  
Respiration, artificial.  
Optical fibers.  
Tracheobronchomegaly.  
Positive-pressure respiration.

## PALAVRAS-CHAVE:

Broncoscopia.  
Respiração artificial.  
Fibras ópticas.  
Traqueobroncomegalia.  
Respiração com pressão positiva.

## ABSTRACT

**CONTEXT:** Mounier-Kuhn syndrome is a rare congenital condition with distinct dilatation and diverticulation of the tracheal wall. The symptoms may vary and the treatment usually consists of support.

**CASE REPORT:** The patient was a 60-year-old male with recurrent hospital admission. He was admitted in this case due to dyspnea, cough and sputum production. An arterial blood sample revealed decompensated respiratory acidosis with moderate hypoxemia. A chest computed tomography (CT) scan showed dilatation of the trachea and bronchi, tracheal diverticula and bronchiectasis. Flexible bronchoscopy was performed, which revealed enlarged airways with expiratory collapse. Furthermore, orifices of tracheal diverticulosis were also detected. Non-invasive positive pressure ventilation (NPPV) was added, along with long-term oxygen therapy. At control visits, the patient's clinical and laboratory findings were found to have improved.

**CONCLUSION:** Flexible bronchoscopy can be advocated for establishing the diagnosis and non-invasive mechanical ventilation can be used with a high success rate, for clinical wellbeing in Mounier-Kuhn syndrome.

## RESUMO

**CONTEXTO:** A síndrome de Mounier-Kuhn é uma condição congênita rara com dilatação e diverticulação distintas da parede traqueal. Os sintomas podem ser variáveis e o tratamento geralmente é de suporte.

**RELATO DE CASO:** Paciente do sexo masculino, de 60 anos, com internação hospitalar recorrente, foi internado neste caso devido a dispneia, tosse e produção de expectoração. A amostra de sangue arterial revelou acidose respiratória descompensada, com hipoxemia moderada. A tomografia computadorizada de tórax mostrou dilatação da traqueia e brônquios, divertículos traqueais e bronquiectasias. Realizou-se broncoscopia flexível, que revelou aumento das vias aéreas com colapso expiratório. Além disso, também foram detectados orifícios de diverticulose traqueal. Foi adicionada ventilação com pressão positiva não invasiva (NPPV) juntamente com a oxigenoterapia a longo prazo. Foram verificadas melhoras dos resultados clínicos e laboratoriais do doente nas visitas de controle.

**CONCLUSÃO:** A broncoscopia flexível pode ser defendida para estabelecer o diagnóstico, e a ventilação mecânica não invasiva pode ser utilizada com alta taxa de sucesso, para bem-estar clínico, na síndrome de Mounier-Kuhn.

## INTRODUCTION

Mounier-Kuhn syndrome is a rare congenital condition characterized by distinct dilatation, and often by diverticulation of the trachea and central bronchi, in association with thinning or atrophy of the elastic tissue.<sup>1,2</sup> The diagnosis is established through radiological and bronchoscopic findings. The treatment usually consists of support (Table 1).<sup>3,4</sup>

We report a male case of Mounier-Kuhn syndrome that was diagnosed through observation of orifices of tracheal diverticula and tracheobronchomegaly, using flexible bronchoscopy (FB). The case was successfully treated by means of non-invasive mechanical ventilation (NIMV).

## CASE REPORT

A 60-year-old cachectic male was admitted to our hospital with complaints of dyspnea and cough. The patient had previously been diagnosed with chronic obstructive pulmonary disease (COPD), bronchiectasis and bullous emphysema, approximately 10 years earlier in another hospital. On that occasion, he had been treated with long-acting beta agonist, long-acting muscarinic antagonist and inhaler corticosteroid. He had a 20 pack-year smoking history and, for years, he had had recurrent admissions with pulmonary tract infections. Physical examination revealed decreased breathing sounds, across both sides of the lungs. Inspiratory coarse crackles were observed with finger-clubbing changes.

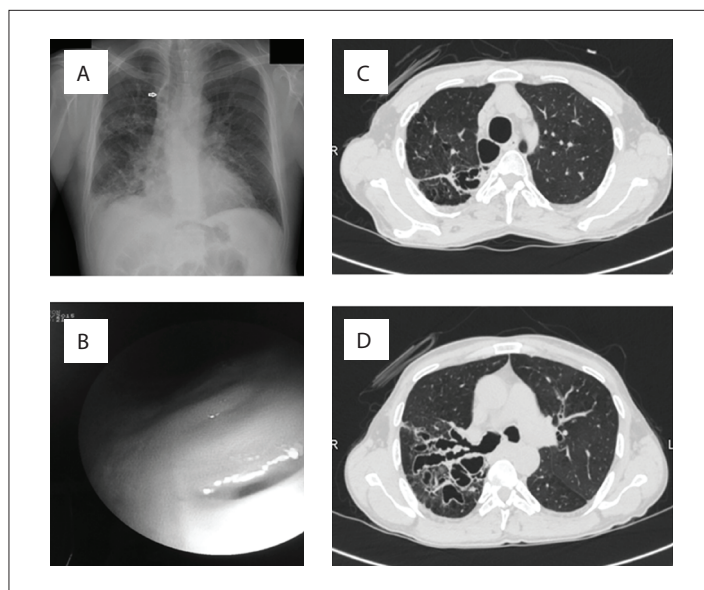
A chest X-ray showed right paratracheal lucency, ill-defined opaque areas, reticular dense areas and cystic lesions predominantly in the right middle and lower zones (Figure 1A). Pulmonary function testing revealed a mainly restrictive but also obstructive pattern with forced expiratory volume in one sec (FEV1) of 2.01 liters (53%), forced vital capacity (FVC) of 2.49 liters (59%) and FEV1/FVC of 88%. Arterial blood gases showed hypoxemia and hypercapnia with respiratory acidosis (pH 7.30; PaO<sub>2</sub> 50 mmHg; PaCO<sub>2</sub> 69 mmHg; HCO<sub>3</sub> 28.3 mmol/l; and SaO<sub>2</sub> 82%).

**Table 1.** Search of the literature in medical databases for case reports on Mounier-Kuhn syndrome. The search was last updated on February 3, 2017

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	(Mounier Kuhn [Title]) AND tracheobronchomegaly [Title]	42	36
MEDLINE (via PubMed)	(Mounier Kuhn [Title]) AND tracheobronchomegaly [Title] case reports [Publication Type]	31	29
Embase (via Elsevier)	(Mounier Kuhn [Title]) AND tracheobronchomegaly [Title] case reports [Publication Type]	6	5
LILACS (via Bireme)	(Mounier Kuhn [Title]) AND tracheobronchomegaly [Title] case reports [Publication Type]	1	1

Administration of nasal oxygen at 2 liters/min and NIMV were started. The inspiratory and expiratory pressures were started as 15/5 mmHg and then were titrated to 20/5 mmHg. ST (spontaneous/timed) mode was selected because of the patient's insufficiency of inspiratory effort. Over the next few days, oxygenation improved and this revealed compensated respiratory acidosis with NIMV (pH 7.38; PaO<sub>2</sub> 61 mmHg; PaCO<sub>2</sub> 55 mmHg; HCO<sub>3</sub> 27.5 mmol/l; and SaO<sub>2</sub> 92%), which probably reflected improvements in tidal volume and reduction in airway expiratory collapse. Diverticulum orifices on the lateral tracheal wall (Figure 1B) and tracheal/main stem bronchial enlargement were noted, with expiratory collapse of the airways, seen using flexible bronchoscopy. Bronchial brushing was performed on the right upper lobe posterior segment and right lower lobe apical segment. After specimen collection, bronchial lavage was performed on both sides using n-acetyl cysteine solution to facilitate expectoration, also known as bronchial toilet. The cytological examination of these materials was negative for malignancy and/or acid-fast bacilli (AFB) staining. Common bacterial and AFB cultures were also negative.

Chest computed tomography was also performed. This demonstrated abnormally dilated trachea, with bilateral main stem bronchi and two diverticula arising from the intrathoracic trachea. Bilateral cystic bronchiectasis was present predominantly in the right middle and lower lobe and mosaic attenuation was observed in lung fields bilaterally (Table 2 and Figures 1C and D).



**Figure 1.** A. Chest X-ray showing ill-defined opaque areas, reticular dense areas and cystic lesions, predominantly in the right middle and lower zone; and also right paratracheal lucency (arrow). B. Diverticulum orifices on the tracheal wall seen in bronchoscopy. C and D. Chest computed tomography showing dilated trachea and bilateral main stem bronchi diverticula arising from the intrathoracic trachea; bilateral cystic bronchiectasis presenting predominantly in the right middle and lower lobe.

Mucolytic treatment and physical rehabilitation therapy including postural drainage were arranged. Long-term oxygen and NIMV treatment were planned for home management. Pneumococcal and influenza vaccination were also suggested, to avoid recurrent infections. Regular follow-up visits were planned. The patient was discharged and has been doing well, with oxygen saturation increased to 89%. Furthermore, the patient has not had any serious complaints again, at follow-up visits.

## DISCUSSION

Mounier-Kuhn syndrome (MKS) is a rare congenital condition characterized by dilatation of airways, tracheal diverticulosis and bronchiectasis, associated with thinning or atrophy of the elastic tissues. Numerous diverticula between the tracheal cartilages and bulging dilatations in the posterior wall of the trachea may be present and are characteristic of MKS. It is assumed that these are non-muscular segments protruding between the tracheal cartilages. Histological findings of enlarged airways were described in 1987, but the first clinical description was made in 1932. The etiology of these findings remained uncertain, but congenital atrophy of smooth muscle and elastic tissue of the trachea and main bronchi was observed. Dilatation of the trachea and proximal bronchi causes impaired clearance of secretions, inefficient cough, persistent airway inflammation and subsequent distal bronchiectasis and/or emphysema.<sup>1,2</sup> In the evaluation on the patient of the present report, no assessment of enlargement of the airways was performed at the time of his COPD/bronchiectasis diagnosis.

To date, the diagnosis of MKS is purely radiological. If the transverse diameter of the trachea exceeds 3.0 cm, right bronchus 2.4 cm and left bronchus 2.3 cm, the diagnosis is established.<sup>3</sup> Other tracheal size thresholds include 2.5 cm for men and 2.1 cm for women.<sup>1</sup> Radiological findings need to be supported by clinical findings. Radiologically, MKS is manifested not only through dilatation of the tracheobronchial system, but also through protrusion of the redundant musculomembranous tissue between the cartilaginous rings.<sup>3,4</sup>

MKS has three subtypes. In type 1, there is slight symmetrical dilation of the trachea and main bronchi. In type 2, the dilation and diverticula are distinct. In type 3, diverticular and saccular

structures extend to the distal bronchi.<sup>2,4</sup> Our patient fitted well into the third subtype, with presence of saccular changes away from the trachea (Table 2).

MKS is frequently seen in middle-aged men, and most of the patients are smokers.<sup>1,2</sup> Most of the cases are sporadic, but familial cases have been described, with possible recessive inheritance.<sup>5</sup> This patient was a smoker but had no familial history of cough or excessive sputum among his family members, or any consanguineous marriage.

During flexible bronchoscopy, the increased tracheal and main bronchial diameter can be detected.<sup>1,2</sup> These semicircular folds of mucous membrane with saccular pouches have been described as tracheal or bronchial diverticulosis. Flexible bronchoscopy may easily detect such diverticula. Also, dynamic tracheal collapse may be viewed by means of bronchoscopy and is considered to be the gold standard for diagnosing tracheomalacia.<sup>6</sup> Bronchoscopy is important not only for making the diagnosis, but also for enabling treatment options such as airway stenting.<sup>2,7</sup>

In our patient, the diagnosis of MKS was strongly supported by detection of diverticulum orifices and enlargement of the trachea and main stem bronchi, seen on flexible bronchoscopy. Thus, in this patient, it was important to detect tracheobronchomegaly, rather than bronchiectasis, especially for the course of the management.

The treatment options are usually symptomatic. Mucolytic therapy and physiotherapy have been used to increase separation of the sputum and facilitate expectoration.<sup>2</sup> Lung transplantation has been reported.<sup>1</sup> Expiratory airway collapse may cause serious breathing problems. NIMV has shown promising results in reducing symptoms in several cases, through serving to decrease pulmonary resistance and respiratory work load and improve expiratory flow and symptom control.<sup>2,6,7</sup> In our patient, we used bi-level positive airway pressure to manage both expiratory airway collapse and hypercapnic respiratory failure.

## CONCLUSION

Flexible bronchoscopy can be advocated for establishing the diagnosis of Mounier-Kuhn syndrome and NIMV can be used with a high success rate for clinical wellbeing in cases of this syndrome.

**Table 2.** Patients' airway diameters used for establishing the diagnosis of Mounier-Kuhn syndrome<sup>1</sup>

	Trachea (subcarinal junction)	Trachea (midsternum)	Carina	Right main bronchus	Left main bronchus
Transverse diameter (cm)	2.6* (2.7) <sup>†</sup>	2.6* (2.9) <sup>†</sup> (3.4) <sup>‡</sup> (5.0) <sup>§</sup>	2.1* (3.2) <sup>†</sup>	1.5* (2.2) <sup>†</sup> (2.9) <sup>‡</sup> (3.8) <sup>§</sup>	1.5* (1.8) <sup>†</sup> (2.8) <sup>‡</sup> (3.4) <sup>§</sup>
Antero-posterior diameter (cm)	2.5* (2.5) <sup>†</sup>	2.6* (2.7) <sup>†</sup>	2.9* (2.7) <sup>†</sup>	-	-

\*Shah et al.<sup>1</sup>; <sup>†</sup>Our patient's diameters are shown in parentheses. Some additional patient diameters are also shown in parentheses, from <sup>‡</sup>Celik et al.<sup>3</sup>;

<sup>§</sup>Abdelghani et al.<sup>4</sup>

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# Myalgia-arthralgia syndrome induced by docetaxel in oncology: the wolf disguised as a sheep

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Taxanes are anti-microtubulin drugs that have a broad spectrum of antitumor activity. They are probably the most widely used cytotoxics.<sup>1</sup> Their common adverse effects include bone marrow suppression, hypersensitivity or skin reactions, alopecia and peripheral sensory neuropathy<sup>1</sup>. However, the myalgia-arthralgia syndrome (MAS), which is frequent in daily practice, remains the great unknown. There are no data regarding its incidence or appropriate treatment and this is a matter for concern, since it impacts negatively on patients' compliance.

MAS usually appears within the first hours or days after taxane infusion and patients complain of moderate to severe generalized musculoskeletal pain: sometimes comprising joint and bone pains and at other times neuropathic pain, with sensations of electrical shock and weakness in both legs.<sup>1</sup>

Recently, professionals have become more aware of the relevance of MAS, and this is probably because most protocols in cases of early breast cancer use a sequential regimen with fluorouracil, epirubicin and cyclophosphamide (FEC) followed by docetaxel monotherapy at a dose of 100 mg/m<sup>2</sup>, as opposed to the dose in combination.<sup>2</sup> A recent review with 102 patients<sup>1</sup> reported that around 30% of them suffered from MAS, but did not give definite answers as to why this syndrome is developed or how to treat it adequately. Extended doses of steroids, pregabalin, gabapentin, non-steroidal anti-inflammatories, opioids, etc., have been tried with contradictory results.<sup>3</sup> Unfortunately, MAS has been the most relevant reason for reducing the dose or definitively halting the oncological treatment, and this may place survival outcomes at risk.

We reviewed 100 patients with localized breast cancer treated during 2015 and 2016 in our Department. These received docetaxel at a dose of 100 mg/m<sup>2</sup>. We collected data about the incidence of MAS, rate of discontinuation and dose reduction due to this syndrome. Briefly, 84 patients developed MAS after the first cycle, which was a much higher incidence than expected. They complained of generalized pain and sometimes "shooting pains" in both legs, usually starting 3 or 4 days after the infusion and lasting on average 7 days (range: 4-10 days). Most of these patients had grade 1 or 2 symptoms, but 22% had grade 3 and they needed a dose reduction. Some of them asked for interruption (2%). Initially, those patients were treated with non-steroidal anti-inflammatories, paracetamol and steroids, but none of these helped. Then we decided to try a combination of codeine and paracetamol, or morphine if the patients were intolerant to codeine. With this, the figures changed completely. No further dose modifications were needed, and the patients coped well with the treatment (MAS grade 0-1, but manageable).

In 2018, we completed a prospective study at our department, in which 60 patients receiving docetaxel at 100 mg/m<sup>2</sup> were included. All received a combination of codeine and paracetamol and the instructions to use it immediately if symptoms of MAS appeared. Patients had received adequate education with explanations about what to expect, when and how to treat it immediately. We noted that there was no dose reduction of docetaxel or interruption due to MAS. Our results are very encouraging, because the patients have been able to complete their oncological treatment as planned. We consider it important to share these results with all professionals, and not only oncologists, since many of these patients seek help in the emergency departments when they become very worried about this generally forgotten adverse event.

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## AIM AND EDITORIAL POLICY

### Indexing and scope

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is now published bimonthly by the Associação Paulista de Medicina. It accepts articles in the fields of clinical health science (internal medicine, gynecology & obstetrics, mental health, surgery, pediatrics, epidemiology and public health). Articles will be accepted in the form of original articles, narrative reviews, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

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

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The title page must contain:

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

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

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

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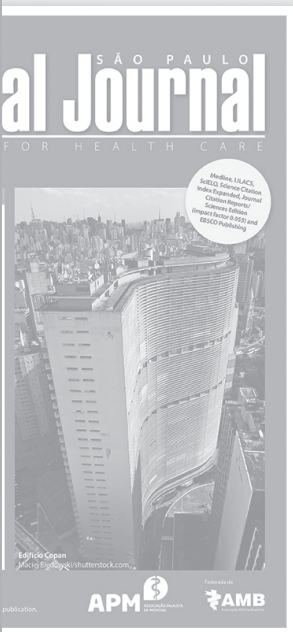
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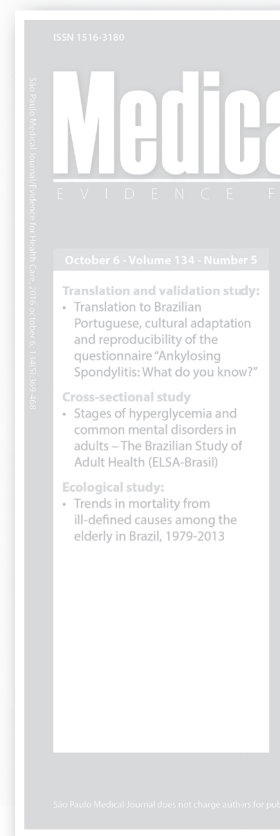
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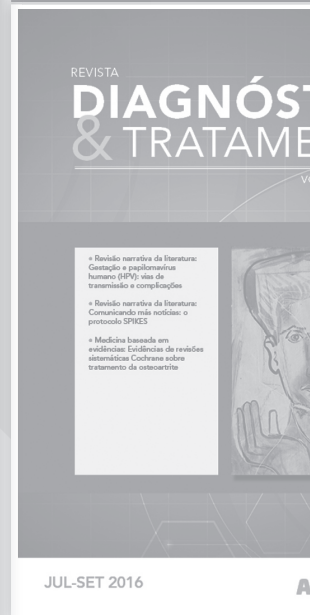
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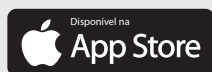
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