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Association between maternal prepregnancy body mass index with offspring cardiometabolic risk factors: analysis of three Brazilian birth cohorts

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Original Article

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Abstract

Evidence suggests that maternal prepregnancy body mass index (BMI) is associated with offspring cardiometabolic risk factors. This study was aimed at assessing the association of maternal prepregnancy BMI with offspring cardiometabolic risk factors in adolescence and adulthood. We also evaluated whether offspring BMI was a mediator in this association. The study included mother–offspring pairs from three Pelotas birth cohorts. Offspring cardiometabolic risk factors were collected in the last follow-up of each cohort [mean age (in years) 30.2, 22.6, 10.9]. Blood pressure was measured using an automatic device, cholesterol by using an enzymatic colorimetric method, and glucose from fingertip blood, using a portable glucose meter. In a pooled analysis of the cohorts, multiple linear regression was used to control for confounding. Mediation analysis was conducted using G-computation formula. In the adjusted model, mean systolic blood pressure of offspring from overweight and obese mothers was on average 1.25 (95% CI: 0.45; 2.05) and 2.13 (95% CI: 0.66; 3.59) mmHg higher than that of offspring from normal-weight mothers; for diastolic blood pressure, the means were 0.80 (95% CI: 0.26; 1.34) and 2.60 (95% CI: 1.62; 3.59) mmHg higher, respectively. Non-HDL cholesterol was positively associated with maternal BMI, whereas blood glucose was not associated. Mediation analyses showed that offspring BMI explained completely the association of maternal prepregnancy BMI with offspring systolic and diastolic blood pressure, and non-HDL cholesterol. Our findings suggest that maternal prepregnancy BMI is positively associated with offspring blood pressure, and blood lipids, and this association is explained by offspring BMI.

Introduction

Mean body mass index (BMI) has increased worldwide, and obesity reached epidemic proportions[1]. In Pelotas, a southern Brazilian city, the prevalence of maternal prepregnancy overweight increased from 22.1% in 1982 to 47.0% in 2015[2]. In the short term, maternal overweight during pregnancy is associated with a higher risk of preeclampsia, gestational diabetes, spontaneous preterm labor, macrosomia, congenital anomalies, stillbirth, unsuccessful breastfeeding, and even maternal death[3-5]. Furthermore, it has also been suggested that maternal overweight in the pregnancy may program the development of cardiometabolic risk factors in the offspring. Maternal prepregnancy BMI would be positively associated with higher offspring BMI, fat mass percentage, and mean levels of metabolic cardiovascular risk factors such as blood pressure, glucose, and cholesterol[6-18].

Concerning the mechanisms for the association of maternal prepregnancy BMI with offspring cardiovascular risk, maternal overweight/obesity during pregnancy would induce changes in fetal metabolism that would have an effect on offspring body composition and the development of metabolic cardiovascular risk factors[19]. Overweight or obese women would have higher glucose, lipids, and fatty acids levels, which may lead to fetal overfeeding and consequently to changes in energy metabolism and the fetal endocrine system, resulting in differences in appetite control, risk of obesity, and cardiometabolic outcomes[20,21]. Furthermore, offspring anthropometric measurements or body composition could be another mechanism for this association. As previously mentioned, offspring of overweight or obese mothers have higher BMI[8,13,14,16], which is positively associated with blood pressure, glucose, and changes in lipid profile[22–24]. Concerning the control for confounding, most of the previously

published studies adjusted their estimates for possible mediators, such as gestational age, birth weight, offspring smoking status, offspring schooling, offspring physical activity, age, and maturation stage[8,9,14,15,17,18]. By adjusting the estimates to possible mediators, a causal pathway is blocked, the total effect underestimated, and a collider bias is introduced[25]. Some studies may be susceptible to residual confounding because they have not adjusted their estimates for known confounding factors, such as socioeconomic status[13,26]. It is important to distinguish between confounder and mediator. A confounder is a variable that has a direct effect on the exposure and the outcome, whereas a mediator is caused by the exposure and is associated with the outcome, i.e. the mediator is in the causal pathway between exposure and outcome[27,28].

To our knowledge, only one study assessed the possible mediators for the association of maternal prepregnancy BMI with offspring cardiometabolic risk factors. Daraki *et al* evaluated the role of gestational weight gain, birth weight, breastfeeding duration, and TV watching as possible mediators[8]. The possible mediators were included in the multiple linear regression model and adjustment for these variables did not change substantively the regression coefficients[8]. This approach has been criticized because it does not adjust for confounders of the mediator – outcome association and does not consider a possible interaction between exposure and the mediator[27].

The present study was aimed at evaluating the association of maternal prepregnancy BMI with offspring blood pressure, random blood glucose, and non-HDL cholesterol in adolescence and adulthood in three Brazilian birth cohorts. We also estimated the indirect effect of offspring BMI in the association of maternal prepregnancy nutritional status with metabolic cardiovascular risk factors using statistical methods that adjust for mediator-outcome confounders.

Methods

Study design and participants

In 1982, 1993, and 2004, all maternity hospitals in Pelotas, a southern Brazilian city, were daily visited and all births identified. Those live births whose mothers lived in the urban area of the city were examined, and their mothers were interviewed soon after delivery (1982, $n = 5914$, 1993, $n = 5249$, and 2004, $n = 4231$). These subjects have been followed up for several times at different ages. In the present study, we used data from the last follow-up of each cohort, which was carried out at mean ages of 30.2 (SD: 0.3), 22.6 (SD: 0.3), and 10.9 (SD: 0.3) years of age for the 1982, 1993, and 2004 cohorts, respectively. In these visits, subjects were invited to visit the research clinic to be interviewed and examined.

Maternal prepregnancy BMI

In the three cohorts, information on maternal prepregnancy weight was gathered from prenatal cards or when absent by self-report in the perinatal visit. With respect to height, in 1982 and 1993, the mothers were measured by the hospital staff and this data were retrieved from the hospital records, whereas in 2004, the mothers were measured at home in the 3-month visit by the research team. In all cohorts, height was evaluated using a locally made portable stadiometer with a precision of 1 mm. As suggested by the World Health Organization (WHO), those mothers with a BMI < 18.5 kg/m^2 were considered as underweight, normal weight was defined by a BMI between 18.5 and 24.9 kg/m^2, overweight by a BMI ≥ 25.0 and ≤ 29.9 kg/m^2 and a BMI ≥ 30.0 kg/m^2 defined the presence of obesity[29].

Metabolic cardiovascular risk factors

In the three cohorts, blood pressure was measured using an automatic device, model HEM-705CPINT – Omron, on the left arm, with a cuff appropriate for arm circumference. Two measurements were taken with the subject seated, one at the beginning of anthropometry and other at the end, and the mean of the two readings (in mmHg) was used in the analyses.

Blood cholesterol and glucose were evaluated only for the 1982 and 1993 cohorts, using plasma or serum that was collected during the visit and was stored at −80ºC. Total and HDL cholesterol were measured using an enzymatic colorimetric method, with a chemical analyzer BS 380 Mindray. Non-HDL cholesterol (mg/dl) was calculated as the difference between total and HDL cholesterol. Random blood glucose (mmol/l) was measured from fingertip blood, using a portable glucose meter (Accu-Check Advantage – Roche). Information on the time of the last meal and the blood collection were recorded so that the time elapsed since the last meal could be calculated.

Confounders and mediators

The following variables, measured in the perinatal study, were considered as possible confounders: maternal schooling in complete years (0–4, 5–8, 9–11, ≥ 12), family income at birth in tercile, maternal age in years (<20, 20–25, 26–30, >30), parity (1, 2, ≥3), and maternal smoking during pregnancy (No/Yes).

Offspring BMI at the last visit was considered as a possible mediator. Cohort members were weighed to the nearest 0.1 kg using a scale coupled to the BodPod (COSMED, Chicago, USA) with a maximum of 150 kg, and height was measured with a portable stadiometer (SECA 240; SECA, Birmingham, UK). BMI was calculated by dividing the weight by the squared height in meters (kg/m^2).

In the mediation analysis, offspring schooling in complete years (0–4, 5–8, 9–11, ≥ 12), family income at the last visit, physical activity, and diet were considered as post-confounders. Physical activity was measured using GENEActiv accelerometer (ActivInsights, Kimbolton, UK) for the 1982 cohort, and ActiGraph, wGT3X-BT, wGT3X, and ActiSlee models (ActiGraph, USA) for the 1993 and 2004 cohorts. Accelerometers were worn for 7 consecutive days and we evaluated the time spent in moderated and vigorous physical activity. Diet was assessed with a food frequency questionnaire, and the Block score was used to estimate the intake of fiber and fat.

Statistical analysis

Analyses were carried out using Stata version 14.0. Analysis of variance (ANOVA) was used to compare means and multiple linear regression to adjust for possible confounders (family income at birth, maternal schooling, maternal age, parity, maternal smoking during pregnancy, and cohort membership).

Figure 1 illustrates the potential pathways between maternal prepregnancy BMI with offspring non-HDL cholesterol, systolic and diastolic blood pressure. Mediation analysis was carried out using G-computation formula to decompose the total effect into natural direct and indirect effects of maternal prepregnancy BMI on offspring metabolic cardiovascular risk factors. Standard errors for mediation analyses were calculated using bootstrapping

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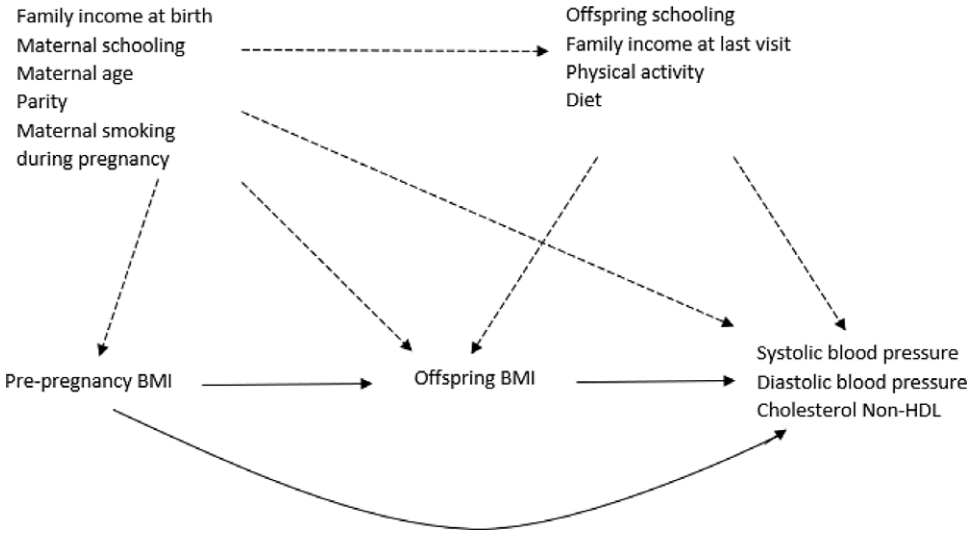

Fig. 1. Directed acyclic graph showing potential pathways between maternal prepregnancy BMI with offspring non-HDL cholesterol, systolic and diastolic blood pressure.

with 10,000 simulations. Separate models were fitted for each offspring outcome. The data from the three cohorts were pooled, analyzed, and all models were adjusted for base confounders (family income at birth, maternal schooling, maternal age, parity, maternal smoking during pregnancy, and cohort membership), and post-confounders (offspring schooling, family income at last visit, physical activity, and diet). A term for exposure–mediator interaction was included in all models. Statistical significance was set at heterogeneity and trend p-values < 0.05, and all tests were two-tailed. The beta coefficients were converted into outcome units (mmHg, mg/dl ,and mmol/l) to facilitate understanding and interpretation of results.

This study was carried out according to guidelines established in the Declaration of Helsinki and all procedures involving human subjects were approved by the Research Ethics Committee of the School of Medicine, Federal University of Pelotas.

Results

Table 1 shows that the prevalence of maternal prepregnancy obesity increased from 4.3% in 1982 to 6.2% in 2004, maternal schooling increased across the three cohorts, whereas the prevalence of maternal smoking in the pregnancy slightly decreased from 35.6% in 1982 to 28.6% in 2004. Mean birth weight was similar in the three cohorts, but the prevalence of preterm birth increased from 6.2% in 1982 to 13.3% in 2004. The mean systolic blood pressure was 121.1 mmHg (SD.: 13.8) for the 1982 cohort, 123.4 mmHg (SD: 13.7) for the 1993 cohort, and 112.5 mmHg (SD: 11.1) for the 2004 cohort. Mean non-HDL cholesterol was 132.4 mg/dl (SD: 36.7) for the 1982 and 110.4 mg/dl (SD: 32.9) for the 1993.

Table 2 shows that after controlling for confounding, systolic blood pressure was associated with maternal prepregnancy BMI. Offspring of overweight or obese mothers had a higher mean systolic blood pressure than those from normal-weight mothers, with mean differences of 1.25 mmHg (95% CI: 0.45; 2.05) and 2.13 mmHg (95% CI: 0.66; 3.59), respectively. For diastolic blood pressure, the magnitude of the association increased after adjusting for confounding, and a positive association was already observed in the crude analyses. Mean random blood glucose was slightly higher among offspring of obese mothers, but the confidence interval included the reference. Therefore, the observed difference may have been due to the random variation. Non-HDL cholesterol among offspring of overweight and obese mothers was 2.70 mg/dl (95% CI 0.25; 5.15) and 4.22 mg/dl (95% CI − 0.58; 9.02) higher, respectively, than that among those from normal-weight mothers.

Table 3 shows that offspring BMI captured the effect of maternal prepregnancy nutritional status on non-HDL cholesterol, and on systolic and diastolic blood pressure. The natural indirect effect of offspring BMI was 1.91 mmHg (95% CI 1.63; 2.19) for mean systolic blood pressure, 1.21 mmHg (95% CI 1.02; 1.40) for mean diastolic blood pressure, and 3.14 mg/dl (95% CI 2.55; 3.72) for mean non-HDL cholesterol. The controlled direct effect was similar between the different levels of the mediator, suggesting that there was no interaction.

Discussion

In the present study, maternal prepregnancy BMI was positively associated with offspring systolic and diastolic blood pressure and non-HDL cholesterol, whereas we did not observe an association with blood glucose. The mediation analysis showed that offspring BMI captured the total effect of maternal prepregnancy BMI.

Concerning the mediation analysis, as expected, offspring BMI was a mediator of the association between maternal prepregnancy BMI and offspring outcomes. Since BMI is positively associated with blood pressure and lipids[30], and it has also been reported that maternal prepregnancy nutritional status is associated with offspring BMI[8,13,14,16,31]. We tested whether these associations were modified by breastfeeding and offspring BMI; however, we did not observe any indication of interaction by these variables. In a previously published study, we evaluated the association of maternal prepregnancy BMI with offspring BMI in adolescence and early adulthood. Offspring BMI was positively associated with maternal prepregnancy BMI, even after controlling for confounders[16]. Mean BMI of offspring of obese mothers was 0.65 kg/m² (95% CI: 0.48; 0.81) higher than that among those of normal-weight mothers in 1982 Pelotas birth cohort (mean age at anthropometric assessment: 30.2 years), the mean difference for 1993 Pelotas birth cohort, at a mean age of 22.6 years, was 0.65 kg/m² (95% CI: 0.45; 0.85), and for 2004 Pelotas birth cohort (mean age at anthropometric assessment: 10.9) was 0.83 kg/m² (95% CI: 0.64; 1.01). And, we also observed that offspring diet and physical activity did not modify this association[16].

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Table 1. Characteristics of the studied population of three Pelotas birth cohorts, Rio Grande do Sul State, Brazil

Socioeconomic variables at birth	Cohort 1982 N (%)	Cohort 1993 N (%)	Cohort 2004 N (%)
Maternal schooling in years			
0–4	1959 (33.3)	1185 (27.3)	464 (14.8)
5–8	2444 (41.4)	2000 (46.1)	1269 (40.6)
9–11	652 (11.1)	787 (18.1)	1053 (33.7)
≥ 12	834 (14.2)	370 (8.5)	340 (10.9)
Maternal age in years			
< 20	912 (15.5)	788 (18.1)	619 (19.6)
20–25	2193 (37.2)	1470 (33.8)	1051 (33.4)
26–30	1485 (25.2)	1080 (24.9)	686 (21.7)
>30	1305 (22.1)	1008 (23.2)	799 (25.3)
Maternal variables			
Maternal nutritional status prepregnancy			
Underweight	388 (7.8)	412 (9.8)	181 (8.3)
Normal weight	3486 (70.3)	2992 (70.8)	1470 (67.5)
Overweight	875 (17.6)	669 (15.8)	391 (18.0)
Obese	212 (4.3)	151 (3.6)	136 (6.2)
Parity			
1	2318 (39.3)	1561 (35.9)	1254 (39.8)
2	1653 (28.1)	1234 (28.4)	849 (26.9)
≥ 3	1923 (32.6)	1552 (35.7)	1052 (33.3)
Maternal smoking during pregnancy			
No	3797 (64.4)	2864 (65.9)	2253 (71.4)
Yes	2099 (35.6)	1483 (34.1)	903 (28.6)
Birth conditions			
Gestational age			
< 37 weeks	291 (6.2)	426 (11.0)	420 (13.3)
≥ 37 weeks	4367 (93.8)	3446 (89.0)	2727 (86.7)
Birth weight (g)			
< 2500	570 (9.7)	425 (9.8)	287 (9.1)
2500–<3000	1517 (25.8)	1156 (26.8)	811 (25.7)
3000–<3500	2190 (37.1)	1694 (39.0)	1264 (40.1)
≥ 3500	1614 (27.4)	1059 (24.4)	793 (25.1)
Offspring cardiometabolic risk factor (SD)			
Mean age at outcome assessment (years)	30.2 (0.3)	22.6 (0.3)	10.9 (0.3)
Mean systolic blood pressure (mmHg)	121.1 (13.8)	123.4 (13.7)	112.5 (11.1)
Mean diastolic blood pressure (mmHg)	75.3 (9.3)	72.8 (8.6)	65.7 (8.6)
Mean glucose	89.5 (26.0)	89.9 (22.0)	–
Mean cholesterol non-HDL	132.4 (36.7)	110.4 (32.9)	–

We failed to observe an association of blood glucose with maternal prepregnancy BMI. Wander *et al* also did not observe an association between maternal prepregnancy BMI with offspring blood glucose at a mean age of 32 years[11]. Similar finding was reported by Tan *et al* among 12-year-old subjects, when comparing the mean blood glucose concentration of offspring whose mothers were overweight or obese with offspring whose mothers were normal weight, but the estimates were not adjusted for confounding factors[9]. On the other hand, Westberg *et al* showed that maternal BMI was negatively associated with 2-hour glucose concentration

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Table 2. Association between maternal prepregnancy nutritional status and offspring cardiometabolic risk factors, a pooled analysis on three Pelotas birth cohorts, Rio Grande do Sul State, Brazil

	Maternal prepregnancy nutritional status				
	Underweight β (95% CI)	Normal weight	Overweight β (95% CI)	Obese β (95% CI)	p-value
Systolic blood pressure (mmHg)[a]					
Crude	0.00 (−1.13; 1.14)	Ref. (0)	0.76 (−0.06; 1.59)	0.48 (−1.04; 2.00)	0.315[†]
Adjusted*	−0.53 (−1.63; 0.57)	Ref. (0)	1.25 (0.45; 2.05)	2.13 (0.66; 3.59)	<0.001[†]
Diastolic blood pressure (mmHg)[a]					
Crude	−0.31(−1.09; 0.48)	Ref. (0)	0.49 (−0.09; 1.06)	1.41 (0.36; 2.47)	0.017[†]
Adjusted*	−0.46 (−1.20; 0.27)	Ref. (0)	0.80 (0.26; 1.34)	2.60 (1.62; 3.59)	<0.001[†]
Glucose (mmol/l)[b]					
Crude	−0.76 (−2.91; 1.39)	Ref. (0)	−0.72 (−2.33; 0.88)	1.02 (−2.15; 4.19)	0.641[†]
Adjusted*	−0.76 (−2.96; 1.44)	Ref. (0)	−0.71 (−2.36; 0.94)	1.12 (−2.11; 4.35)	0.635[†]
Cholesterol non-HDL (mg/d)[b]					
Crude	−1.19 (−4.56; 2.18)	Ref. (0)	2.34 (−0.17; 4.86)	4.73 (−0.24; 9.69)	0.008[‡]
Adjusted*	0.38 (−2.89; 3.64)	Ref. (0)	2.70 (0.25; 5.15)	4.22 (−0.58; 9.02)	0.029[‡]

*Adjusted: family income at birth, maternal schooling, maternal age, parity, maternal smoking during pregnancy, and cohort membership.
[a]Data from three cohorts.
[b]Data from 1982 and 1993 cohort.
[†]Heterogeneity p-value.
[‡]Trend p-value.

Table 3. Total effect, natural direct effect, and natural indirect effect (via offspring body mass index) of maternal prepregnancy body mass index on offspring systolic and diastolic blood pressure, a pooled analysis for the three Pelotas birth cohort studies ($n = 8827$)

Outcome	Mediator	Total effect β (95% CI)	Natural direct effect β (95% CI)	Natural indirect effect β (95% CI)
Systolic blood pressure (mmHg)	Body mass index (kg/m^2)*	1.63 (1.15; 2.11)	−0.28 (−0.77; 0.21)	1.91 (1.63; 2.19)
Diastolic blood pressure (mmHg)	Body mass index (kg/m^2)*	1.05 (0.71; 1.38)	−0.16 (−0.50; 0.18)	1.21 (1.02; 1.40)
Non-HDL cholesterol (mg/dl)	Body mass index (kg/m^2)*	1.49 (−0.50; 3.48)	−1.64 (−3.70; 0.41)	3.14 (2.55; 3.72)

*Offspring body mass index.
Base confounders (family income at birth, maternal schooling, maternal age, parity, maternal smoking during pregnancy, and cohort membership).
Post-confounders (offspring schooling, family income at last visit, offspring physical activity, and offspring diet).

among male offspring, whereas no association was observed among women[7]. In that cohort, participants were aged 62 and the analyses were adjusted for offspring age, BMI, smoking, and leisure time physical activity[7]. As these variables are possible mediators, the adjustment may have introduced a collider bias, and we cannot predict in which direction the measures of association were affected[25]. Concerning cholesterol, similarly to other studies[9,11,12,17], we observed a worse lipid profile among offspring of obese or overweight mothers.

In relation to study strengths, the association of maternal prepregnancy nutritional status with offspring cardiometabolic risk factors was evaluated using information from three birth cohorts, carried out in a southern Brazilian city. And information on maternal anthropometry and confounders were collected just after delivery using standardized methods, minimizing measurement error and reducing the probability of residual confounding and nondifferential misclassification.

As limitations, we can point out that blood samples were not collected during the fasting period. In relation to cholesterol measures, it has been reported that nonfasting blood collection is better for estimating individual cardiovascular risk[32,33]. On the other hand, for blood glucose, the analyses should be carried out with fasting blood. To minimize this limitation, we corrected the estimates for the time since the last meal. Maternal prepregnancy BMI was based on self-reported data for height and prepregnancy maternal weight. However, a validation study based on data from the Brazilian National Health Survey observed a high agreement between self-reported and measured weight, height, and BMI[33]. Furthermore, information on maternal prepregnancy BMI was collected just after delivery, reducing the likelihood of recall bias. Regarding a possible collinearity between the confounding factors, the correlation was not very high among the confounders, decreasing the likelihood of collinearity. Furthermore, even if these variables were collinear, it is unlikely that the magnitude of the association between maternal BMI and offspring cardiovascular risk factors would be biased.

In conclusion, our results showed that offspring BMI explained the association of maternal prepregnancy nutritional status with

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offspring blood pressure and non-HDL cholesterol levels, reinforcing the importance of implementing interventions aimed at reducing the individual's BMI.

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Author's contributions. MSD and BLH participated in all stages from conception, written part, data analysis, discussion of results. AM, ANBM, FCB, FCW, HG, and ISS revised the final version.

Conflicts of interest. The authors declare that they have no conflict of interest.

Ethical standards. This study was carried out according to guidelines established in the Declaration of Helsinki and all procedures involving human subjects were approved by the Research Ethics Committee of the College of Medicine, Federal University of Pelotas.

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