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RESEARCH ARTICLE

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CORRELATION BETWEEN CALCIUM INTAKE AND RISK FACTORS FOR PREECLAMPSIA AND CARDIOVASCULAR RISK

Erica de Brito Pitilin*¹, Simone Kappes¹, Lais Crusaro Pagnussatt¹, Vanessa Aparecida Gasparin², Debora Tavares de Resende e Silva¹, Margarete Dulce Bagatini¹, Patricia Pereira de Oliveira³, Tainara Fornari¹ and Janine Schirmer⁴

¹Federal University of Fronteira Sul. Fernando Machado Avenue, 108E, Centro, Chapecó, Santa Catarina, Brazil;

²State University of Santa Catarina. 680E Beloni Trombeta Zanin Street, Bairro Santo Antônio. Chapecó, Santa Catarina, Brazil; ³Community University of Chapeco Region. 295D Servidão Anjo da Guarda Street, Bairro Efapi. Chapecó, Santa Catarina, Brazil; ⁴Federal University of São Paulo. 754 Napoleão de Barros Street, Vila Clementino. São Paulo, Brazil

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*Corresponding author: Erica de Brito Pitilin

ABSTRACT

Objective: To correlate dietary calcium intake in pregnant women and factors associated with preeclampsia and cardiovascular risk. **Method:** A cross-sectional study carried out in the southern region of the country with 101 pregnant women, from June 2018 to July 2019. **Results:** The daily consumption of calcium in the diet was below the adequate requirement recommended for pregnant women, with a negative correlation for blood pressure systolic blood pressure ($p=0.049$), C-reactive protein ($p=0.033$), body mass index ($p=0.022$) and triglyceride ($p=0.041$) for hypertensive women. On the other hand, the correlation was positive between nutrient consumption and parathyroid hormone in healthy pregnant women. Low calcium intake was also associated with socioeconomic status and obesity. **Conclusion:** The need for increased calcium consumption seems to promote blood pressure regulation in the maternal organism, in addition to contributing to the reduction of inflammatory processes and cardiovascular risk.

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INTRODUCTION

Preeclampsia (PE) is one of the most frequent hypertensive disorders during the gestational period, being responsible for about 40 to 60% of maternal mortality in developing countries (Phipps *et al.*, 2019). Every year, about 60,000 women die in Brazil from complications of these disorders (Hofmeyr *et al.*, 2019). The Brazilian public health system spends more than BRL 22 million to pay for the treatment of hypertensive disorders, characterizing a substantial expense for a developing country (Omotayo *et al.*, 2016). Although the pathogenesis of hypertensive syndromes is not yet fully understood, there is evidence that the main initiating events are placental hypoperfusion and increased production of anti-angiogenic inflammatory mediators, followed by systemic endothelial injury, disseminated vasospasm, generalized tissue hypoperfusion and worsening ischemia. Placenta (Phipps *et al.*, 2019).

There are several factors that increase the risk of developing hypertensive disorders, such as chronic kidney disease, hypertension, obesity, personal history of PE, nulliparity, advanced maternal age, among others (Samimi *et al.*, 2016). Potential mechanisms of hypertensive syndromes seem to be directly related to maternal dietary intake of vitamins, minerals and micronutrients, including calcium (Dubois *et al.*, 2017). Dietary exposures to calcium and the risk of developing these syndromes, especially PE, have been a particular focus of attention in epidemiological intervention studies (Meertens *et al.*, 2018). It is believed that calcium is related to the reduction of the renin-angiotensin system, acting on the balance between sodium and potassium, minimizing vasoconstriction of the smooth muscle of blood vessels, making it proportional to its resistance (Egeland *et al.*, 2017). Among other benefits, calcium is also related to adequate fetal development, blood clotting, weight control and reduced risk of premature births (Marangoni *et al.*, 2016).

Evidences suggest that the nutrient is capable of modulating lipid metabolism and reducing the risk of mortality from cardiovascular diseases (Chan *et al.*, 2013). The American Heart Association guidelines identify that pregnant women, especially those with a history of hypertensive disorder during pregnancy, are at almost twice the risk of cardiovascular diseases, endothelial dysfunction and inflammatory processes, when compared to healthy pregnant women (Tanz *et al.*, 2018). Despite the indication of the benefits of this micronutrient, the dietary calcium intake of pregnant women in low- and middle-income countries, such as Mexico, Brazil, Ecuador, Argentina and African countries, is low, consisting of less than 600 mg per day (Omotayo *et al.*, 2016; Cormick & Belizán, 2019). Even with the daily intake of calcium in the diet, mainly through dairy products, more than a third of pregnant women consume less than the recommended amount of calcium, which contrasts with the average daily intake of American and European pregnant women (Omotayo *et al.*, 2016; Mosha *et al.*, 2017).

In light of the available evidence, there are few studies to date that investigate the relationship between dietary patterns and risk factors for PE and cardiovascular disease in healthy, hypertensive pregnant women (Tanz *et al.*, 2018; Gete *et al.*, 2010). Furthermore, the assessment of cardiovascular prognosis through the characteristics of biomarkers in pregnant women is incipient (Held *et al.*, 2017), justifying this study. Given the limited availability of calcium-rich foods in the dietary habits of pregnant women in developing countries, such as Brazil, this study assumes that low dietary calcium intake may be related to risk factors for the development of PE, as well as for cardiovascular risk, especially in pregnant women with low socioeconomic conditions. This dietary assessment, if incorporated into the clinical practices of nurses, can play a fundamental role in reducing or avoiding complications arising from hypertensive disorders by knowing the benefits of calcium and encouraging its consumption in the diet of pregnant women during prenatal care. Although obstetric care presupposes interdisciplinary and team work for the integrality of actions, the nurse, as a leader and health promoter, can contribute to a socially relevant work, being able to provide subsidies for the reorganization of services aimed at women in the pregnancy period. Within the scope of primary health care. In this context, this study aimed to correlate dietary calcium consumption in pregnant women and factors associated with preeclampsia and cardiovascular risk.

METHOD

This is a cross-sectional study carried out with 101 pregnant women in the southern region of the country, from June 2018 to July 2019. The western territory of Santa Catarina chosen for the development of the research is a pole of economic and industrial development and a reference in actions of health in the great west of the state of Santa Catarina, composing the region of the Great Frontier of Mercosul (Meso Mercosul). The pregnant women were invited to participate in the research during the prenatal consultation. The selection of participants took place according to the following inclusion criteria: for hypertensive pregnant women diagnosed with gestational hypertension after the 20th week of pregnancy without associated proteinuria, single pregnancy, absence of fetal malformation, absence of preexisting clinical conditions and who did not use drugs that could interfere with calcium absorption (eg, corticosteroids, thiazides, and thyroid hormones). Healthy pregnant women were matched according to gestational age and maternal age to minimize or eliminate the confounding effect. To obtain the gestational age, the one recorded in the medical record was adopted. All pregnant women were primigravidae. Participants who had polyhydramnios, severe anemia and abnormal umbilical artery Doppler were excluded from the study. To determine the sample size, the estimated number of hypertensive pregnant women in the year prior to collection was considered, the difference between the means of the groups of 8% in the reduction of systolic and diastolic blood pressure and proteinuria, 4% for secondary outcomes, error type I (α) of 0.05%, ratio 1:1 and a study power of 80% (Hofmeyr *et al.*, 2019). The final sample resulted in

101 pregnant women (51 hypertensive and 50 healthy pregnant women). Pregnant women who met the inclusion criteria were instructed to attend the day and time scheduled by the researchers, fasting for 12 hours, for clinical evaluation and collection of laboratory tests. The clinical evaluation consisted of the application of a health questionnaire and a food recall; performing anthropometric measurements; assessment of blood pressure and fetal heart rate (BCF); measurement of uterine height (UA) and collection of blood and urine for laboratory analysis. The applied questionnaire contained demographic and socioeconomic variables (age, education and income), behavioral and health (physical activity practice, nutritional status), complications in the current pregnancy (hypertensive peak, vaginal bleeding, urinary tract infection, among others) and consumption food (assessed from the information recorded through the 24-hour food recall – R24h – from the day before the appointment). All food recalls were applied using the Multiple-Pass Methods (MPM), according to which the interviewer conducts the interview through food lists by time of day and meals (Moshfegh *et al.*, 2008). This method reduces the bias of the dietary measure, as it helps the interviewee to remember the food of the previous day. Information on drinks consumed was also collected in the recall. The estimate of the usual calcium intake was calculated using the dietWin® software, version 2008. For the inclusion of values, the quantification of the foods was performed according to the Brazilian Food Composition Table (TACO) and the Dietary Reference Intakes (DRI) (Raper *et al.*, 2004). The Estimated Average Requirement (EAR) values for calcium intake by adult pregnant women was 800mg/day, used as a cutoff point (Barquera *et al.*, 2009). The EAR is the estimate of the average daily intake of nutrients needed to meet the needs of half of healthy individuals at a given stage of life and gender, being the most appropriate cut-off point to estimate the occurrence of inadequate intake in population groups.

The probability of dietary calcium inadequacy was determined based on the Dietary Reference Intakes, calculating the difference between the individual observed intake and the Estimated Average Requirement (EAR). The clinical evaluation was performed according to the WHO recommendations and guidelines on prenatal care (World Health Organization, 2016). Blood pressure measurement was standardized according to the recommendations of the British Hypertension Society (BHS) (National Institute for Health and Care Excellence, 2019). In view of the hypertensive peak results (systolic blood pressure – SBP > 160mmHg and diastolic blood pressure – DBP > 110mmHg) observed in two consecutive measurements, the pregnant women were referred to the referral service. Nutritional status was classified using the patient's body weight and height according to the body mass index (BMI), adjusted by gestational week, according to the WHO criteria for evaluation in pregnant women (World Health Organization, 2010). Therefore, body weight was measured with the pregnant woman barefoot and without adornments, using a portable digital scale model HCM 5110 M (GAMA Italy Professional, San Pietro in Casale, Italy) with a capacity of 150kg and sensitivity of 100g, having been calibrated before fieldwork. The portable stadiometer used had a maximum capacity of 200 cm and a resolution of 1 mm. All interviewees were weighed and measured following the standard procedure described in the literature (Lohman *et al.*, 2000).

After birth, research team members extracted data on neonatal outcomes from hospital records (weight and gestational age of the newborn). Aiming at the correlation between calcium and risk factors for preeclampsia and cardiovascular risk, the patients in this study underwent a set of complementary tests, which included the following laboratory measurements: creatinine, urea, proteinuria, parathyroid hormone (PTH), ionized calcium, ultra-sensitive C-reactive protein (hs-CRP), triglycerides, total cholesterol and fractions (low-density lipoprotein – LDL-c; high-density lipoprotein – HDL-c). For these dosages, the analytical procedure standardized in the laboratory was used, in accordance with the protocol defined by the manufacturer of the commercial kits used for each specific exam. Blood samples were collected by the team of researchers and then forwarded to the research support laboratory for further analysis.

The cardiovascular and PE risk factors were those proposed by the WHO, such as maternal age, sedentary lifestyle, nutritional status, blood pressure level, proteinuria, C-reactive protein, dyslipidemia, among others (World Health Organization, 2012). Data were stored and analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0. Descriptive data analysis was used to characterize the population studied. For continuous variables, mean and standard deviation were calculated and, for categorical variables, frequency and percentage. Data normality was tested by the Shapiro-Wilk test and homogeneity of error variances by the Levene test. Analytical statistics were performed using the t test, Pearson's correlation and one-way ANOVA. Differences in which the probability of rejecting the null hypothesis was less than 5% ($p < 0.05$) were considered statistically significant. Data collection was only started after the research project was approved by the Research Ethics Committee under opinion 2,659,764/2018.

All study participants signed the Free and Informed Consent Form (FICT). The research protocol was submitted to the National Council for Scientific and Technological Development (CNPq) and received financial support, according to the notice issued by the Ministry of Science, Technology, Innovations and Communications/National Council for Scientific and Technological Development (MCTIC/CNPq). 28/2018 – Universal and by the scholarship program of the Fund to Support the Maintenance and Development of Higher Education (FUMDES).

RESULTS

The mean age of the pregnant women in this study was 30.3 years (SD 5.1 years) and the mean dietary calcium intake was lower than the estimated adequate need proposed by the guidelines (DRI) for pregnant women, especially for those with hypertension (Table 1).

Table 1. Mean food consumption and the estimated mean adequate need for calcium in the diet of healthy and hypertensive pregnant women proposed by the DRI

Calcium (mg/day)	n	Consumption Mean (SD)	EAR Mean (SD)	p - value
Hypertensive pregnant woman	51	652.68 (426.7)	-127.52 (454.3)	0.049
Healthy pregnant	50	831.08 (565.4)	31.08 (565.4)	

t-student

Table 2. Average dietary calcium intake and demographic, economic and health characteristics of healthy pregnant and hypertensive pregnant women (HPW)

	Dietary calcium (mg/day)		p-value	Healthy pregnant (n=50)		p-value
	HPW (n=51) n (%)	Mean (SD)		n (%)	Mean (SD)	
Age group			0.004			0.000
20 a 29 years	24 (48)	459.3 (234.7)		30 (60)	609.8 (404.4)	
30 a 39 years	27 (52)	792.6 (487.6)		20 (40)	1.162.9 (617.8)	
Gestational age			0.386			0.548
13 ^a a 27 ^a weeks	34 (66)	595.3 (409.8)		26 (52)	877.8 (594.7)	
> 28 ^a weeks	17 (34)	705.1 (439.3)		24 (48)	780.4 (539.9)	
Salary			0.041			0.859
≤ 4 salary	39 (78)	598.4 (420.7)		20 (40)	813.3 (643.3)	
> 4 salary	12 (22)	754.0 (408.0)		30 (60)	842.9 (518.3)	
Years os study			0.036			0.090
< 8 years	18 (36)	538.3 (340.1)		5 (10)	802.6 (560.5)	
≥ 8 years	33 (64)	685.7 (453.7)		45 (90)	1.087.4 (607.9)	
Physical activity			0.224			0,766
Yes	20 (40)	543.8 (401.5)		32 (64)	849.1 (618.8)	
No	31 (60)	691.9 (426.4)		18 (36)	798.8 (470.6)	
Complications			0.725			0,978
Yes	29 (54)	652.2 (420.0)		15 (30)	827.6 (538.0)	
No	22 (46)	609.7 (425.8)		35 (70)	832.5 (584.4)	
Nutritional status			0.043*			0,053
Adequate	5 (10)	806.6 (554.4)		20 (40)	1.370.4 (758.7)*	
Overweight	7 (12)	659.0 (545.5)		25 (50)	835.1 (588.0)	
Obesity	39 (78)	602.5 (385.6)*		5 (10)	691.2 (411.6)	

Test t / * Anova – pos hoc Tukey.

Table 3. Correlation of dietary calcium intake with risk factors for PE and cardiovascular disease, according to clinical and laboratory variables in healthy pregnant and hypertensive pregnant women (HPW)

	HPW			Healthy pregnant			
	Mean (SD)	r	p – value*	Mean (SD)	r	p – value*	p-value [#]
Clinical variables							
SBP, mmHg	135.5 (14.2)	- 0.28	0.049*	109.6 (7.5)	0.14	0.312	0.000
DBP, mmHg	83.6 (11.3)	0.16	0.267	68.6 (7.0)	0.27	0.057	0.000
BMI, Kg/m ²	32.7 (6.6)	- 0.22	0.022*	26.2 (2.9)	- 0.26	0.052	0.000
Laboratory variables							
Hs- CRP, mg/dl	12.5 (8.4)	- 0.30	0.033*	5.1 (4.1)	0.05	0.686	0.000
Proteinuria, mg/dl	13.8 (19.8)	0.05	0.728	6.4 (2.2)		0.210	0.000
Triglyceride, mg/dl	207.3 (77.1)	-0.18	0.041*	162.8 (63.0)	0.06	0.641	0.002
Cholesterol, mg/dl	220.2 (40.2)	0.16	0.253	227.9 (39.1)	0.04	0.776	0.336
c-HDL, mg/dl	65.8 (16.2)	0.17	0.299	78.7 (18.5)	- 0.14	0.333	0.000
c-LDL, mg/dl	116.0 (36.2)	0.00	0.950	117.2 (35.1)	0.07	0.607	0.869
Creatinine, mg/dl	90.8 (45.3)	- 0.11	0.448	79.8 (23.2)	- 0.15	0.275	0.014
Urea, mg/dl	17.7 (5.7)	0.19	0.165	17.1 (4.3)	0.04	0.457	0.565
PTH, mg/dl	26.8 (16.2)	0.03	0.802	22.9 (10.2)	0.23	0.006*	0.154
Ionized calcium, mg/dl	9.1 (0.6)	0.14	0.329	9.3 (0.4)	0.21	0.132	0.043

*Pearson's Correlation. / [#]t test

The average consumption of dietary calcium and the demographic, economic and health characteristics of pregnant women are described in Table 2. Higher consumption of the nutrient was present in pregnant women aged between 30 and 39 years in both groups. However, lower calcium intake was associated with low income, low education and nutritional status in hypertensive pregnant women. Table 3 shows the correlation between dietary calcium intake and risk factors for PE and cardiovascular disease, according to the analyzed clinical and laboratory variables. There was a negative correlation between nutrient consumption and SBP, hs-CRP, triglyceride and BMI in hypertensive pregnant women. On the other hand, the correlation was positive between calcium and PTH in healthy pregnant women. Neonatal outcomes and the correlation of dietary calcium intake are described in Table 4. There was no significant correlation between nutrient intake and birth weight and gestational age in both groups.

Table 4. Correlation between the mean dietary calcium intake and the birth outcomes of hypertensive pregnant women and healthy pregnant women

	Variable	Mean	SD	p-value
HPW	Weight NB (g)	2.883	0.6	0.547
	Gestational age birth (weeks)	37.4	2.5	0.892
Healthy pregnant	Weight NB (g)	3.219	0.4	0.691
	Gestational age birth (weeks)	38.1	0.7	0.083

Pearson's correlation

DISCUSSION

The results of the present study point to the feasibility of a dietary intake rich in calcium in women with gestational hypertension in minimizing risk factors for PE, as well as cardiovascular risk, corroborating the initial hypothesis of the study. The low calcium intake typical of the diet of pregnant women in low- and middle-income countries was lower in hypertensive pregnant women and contrasts with the daily intake of more than 1,000mg of calcium per day of healthy pregnant women residing in developed countries, evidencing the direct relationship socioeconomic status and dietary pattern (Cormick & Belizán, 2019; Gomes *et al.*, 2016). Inequities in health conditions linked to social hierarchies are worse in the population of vulnerable women with a lack of knowledge about preventive and educational issues (Phipps *et al.*, 2019). Higher consumption of the nutrient was also identified in older pregnant women, assuming better access to knowledge of the benefits of the nutrient, as well as the sources of foods rich in calcium and better financial conditions. The literature demonstrates that the risk of developing diseases of the apparatus is greater in disadvantaged groups (Dubois *et al.*, 2017). The lower dietary intake of calcium in this study was correlated with higher clinical and laboratory parameters, especially in hypertensive pregnant women. Higher SBP presupposes the absence of calcium compensatory mechanisms. Similar findings were found in other studies that identified a reduction in blood pressure levels after a diet rich in calcium (Egeland *et al.*, 2017; Marangoni *et al.*, 2016).

It is noteworthy that arterial hypertension in pregnant women is linked to a higher risk of PE, maternal stroke, dyslipidemia, cardiovascular diseases, premature birth, stillbirth and low birth weight (American College of Obstetricians and Gynecologists, 2019). One of the acceptable biological mechanisms by which calcium can minimize such complications is its role in the release of PTH, which reduces renal renin secretion and glomerular permeability, decreasing peripheral vascular resistance with a consequent decrease in the release of renal function biomarkers, such as urea, creatinine and proteinuria (Behjat Sasan *et al.*, 2017). Such findings reinforce the potential positive effects of calcium since the healthy pregnant

women in this study showed a positive correlation with dietary calcium intake and PTH. Another determining factor identified was the correlation between dietary calcium intake and some cardiovascular risk markers, such as BMI, nutritional status, CRP and triglycerides. In hypertensive pregnant women, the correlation of weight (obesity) was greater in those with low daily food consumption, indicating a pattern in the calcium-deficient diet. The same can be observed in another study, which identified lower body fat in people with higher dietary calcium intake, around 400 mg to 1,000 mg/day, resulting in a reduction of 4.9 kg of body fat in obese individuals (Ismail & Qahiz, 2016). Similar results in the improvement of the metabolic status were observed in other studies, reinforcing the effect of calcium in the modulation of these mechanisms (Egeland *et al.*, 2017). For healthy pregnant women, the association of nutrient consumption was greater for those with adequate weight. The high BMI pattern in hypertensive pregnant women is corroborated in international studies, in which the proportion of obese women increased with the increase in gestational hypertension (Phipps *et al.*, 2019; Dubois *et al.*, 2017). Some theories point to a probable association between dietary calcium intake and body weight regulation, assuming an anti-obesity effect, as there is a strong argument that calcium can modulate lipid metabolism in the adipocyte through the high excretion of fatty acids by the feces, in addition to reducing appetite and potentiating the loss of calories and lipid oxidation (Skowrońska-Jóźwiak *et al.*, 2017). In this study, the correlation between dietary calcium intake and lipid metabolism (triglyceride) was negative, suggesting a low dietary pattern of nutrients with primary and derived sources of calcium, such as legumes and dairy products in hypertensive pregnant women. There is a scarcity of studies about these relationships in our environment, an innovative and relevant aspect of the present study. It is worth mentioning that these pregnant women were, in addition to being hypertensive, obese and sedentary. Although weight loss is discouraged during pregnancy, obesity predisposes to a pro-inflammatory state, being a risk factor for cardiovascular disease. There are several arguments that support the theory that high CRP concentrations are predictive of cardiovascular events, such as acute myocardial infarction and atherosclerosis, and therefore serve as the best available independent marker of cardiovascular risk to date (Held *et al.*, 2017).

In this study, the correlation between dietary calcium consumption and hs-CRP was negative, assuming that low dietary nutrient intake increases inflammatory processes and endothelial dysfunction. Other studies also showed the effects of calcium in reducing hs-CRP in pregnant women with potential risk of complications (Samimi *et al.*, 2016; Peikert *et al.*, 2020). Hs-CRP is the best marker of acute phase response currently available, whose blood concentration increases when there is an indication of inflammatory or infectious processes (Peikert *et al.*, 2020). One of its mechanisms of action is related to the binding capacity of phosphocholine in the wall of some vessels in a calcium-dependent binding (Egeland *et al.*, 2017). It is noteworthy that calcium absorption depends on several other factors, such as vitamin D levels, type of diet, amount of protein ingested, among others (Gomes *et al.*, 2016). Finally, there was no correlation between dietary calcium intake and secondary birth outcomes, which reinforces the argument that low birth weight and prematurity are not related to the dietary patterns of pregnant women. On the other hand, calcium seems to act on inflammatory, endothelial and lipid processes in pregnant women. The assessment of food consumption obtained through the listing of daily portions of food groups aimed to generate more practical information and broaden the debate on ways to generate information based on food consumption for use in health services. Such a feat can facilitate communication between professionals and pregnant women in primary care, making information about adequate and calcium-rich diet clearer and promoting greater adherence on the part of women. However, it was not possible to assess the prevalence of under and overreporting of food consumption, since food intake was compared to examine the likely differences between the two groups, which may be a limitation of the study. However, this was an accessory variable and not the main exposure variable of the research. Furthermore, the method used

to collect the food recall (MPM) minimized the bias of the dietary measurement and memory. The need to increase the dietary intake of daily portions of calcium in the diet of pregnant women is reinforced, as the nutrient can reduce the potential risk of problems related to cardiovascular risk factors and preeclampsia in pregnancy. Therefore, exploring strategies to compensate for nutritional and dietary limitations in this context in clinical practice during the care provided to pregnant women is highly recommended and can be encouraged with multidisciplinary teamwork and articulation with Health Academies, for example.

CONCLUSION

The daily dietary intake of calcium can minimize the risk factors for PE and cardiovascular evidenced by the positive correlation between the intake of the nutrient and the parameters analyzed. A higher nutrient intake was related to lower levels of SBP, BMI, hs-CRP and triglyceride in hypertensive pregnant women and PTH in healthy pregnant women. Low consumption was also associated with age, socioeconomic status and nutritional status. The data point to the need to strengthen the area of care for pregnant women at risk, restructuring services into care networks and ensuring access to quality information on the benefits of calcium, encouraging its daily consumption in the diet. The geopolitical and socioeconomic reality of the pregnant women in this study is present in many communities in the country, which gives rise to a deeper reflection on issues of access to quality nutrition. However, obtaining food composition calculations is a complex process, and must be taken into account when interpreting it for the Brazilian population, since the DRIs were designed for American individuals. It is assumed that, based on the findings of this study, calcium consumption can be encouraged by health professionals who provide care to pregnant women, especially nurses. It should be noted that calcium in the diet is more beneficial to health than supplements, in addition to being easier to absorb. It is suggested that other personalized strategies are needed to distinguish different cardiovascular risk profiles, implying the need for specific modifiable approaches, such as lifestyle and diet changes, weight reduction and physical activity. Longitudinal studies are needed to better elucidate the relationship between nutrition and these risk factors.

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