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Seventeen-year changes in cardiovascular risk factors: A cohort study of southern Brazilian young adults

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ABSTRACT

Aim: The origins of atherosclerosis and subsequent cardiovascular disease are recognized to begin in childhood. Studies involving risk factor screening of children and adolescents can be predictive of future rate trends. This study aimed to evaluate changes in cardiovascular risk factors in asymptomatic individuals followed from age 10–18 years at baseline (1999) to age 27–36 years in 2016.

Methods: This was a prospective cohort study. A total of 156 cohort participants were available for follow-up in 2016 (mean age, 29.9 ± 0.2 years). Data collected in 1999, 2006, and 2016 were analyzed to determine the evolution of cardiovascular risk factors over time. Sociodemographic and behavioral data, body mass index (BMI), waist circumference (WC), blood pressure (BP), lipid profile [total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides], and fasting glucose were assessed.

Results: During a 17-year follow-up, there were significant increases in BMI, WC, total cholesterol, HDL-C, triglycerides, and diastolic BP ($p < 0.001$ – 0.011), but significant reductions in systolic BP, fasting glucose, and physical activity ($p \leq 0.001$). The increase in cardiovascular risk factors was significantly greater in men than in women over time ($p < 0.001$ – 0.032).

Conclusions: Our results show a trend toward worsening of cardiovascular risk factors from childhood/adolescence to adulthood. This should serve as a warning to public health officials about the need for health promotion strategies aimed at beginning preventive measures in childhood and adolescence.

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Introduction

Cardiovascular disease (CVD) is the major cause of death in adults worldwide, and more than three-fourths of these deaths occur in low- and middle-income countries [1]. In Brazil, ischemic heart disease accounted for approximately 350,000 deaths in 2016, with a major economic impact resulting from

the allocation of public resources to prevention and treatment programs [2,3].

Autopsy studies in children and young adults have shown the presence of atherosclerotic lesions that positively and significantly correlated with cardiovascular risk factors in the affected individuals. These include fatty streaks, which may begin

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to form within the aorta in the earliest stages of human development, even before birth, and may subsequently progress to fibrous plaques by the age of 15 years [4–7]. These findings indicate that the process of atherosclerosis and subsequent CVD initiates in early childhood.

Adoption of a healthy lifestyle and control of cardiovascular risk factors can reduce the incidence of complications of CVD and, as the origins of atherosclerosis are recognized to begin in childhood, the concept that prevention of adult CVD should begin in early life gains momentum [4]. Also, modification of risk factors beginning in childhood and young adulthood is known to restore to normal or improve measures of subclinical atherosclerosis in individuals with genetic dyslipidemias or dyslipidemia secondary to obesity [8]. Therefore, children and adolescents at increased risk of premature atherosclerosis should be identified and treated as early as possible to prevent CVD in adulthood and reduce future morbidity and mortality rates [9].

Studies involving risk factor screening of children and adolescents can be predictive of future rate trends [10]. In this scenario, the early identification of risk factors may highlight the evolution of cardiovascular risk factors in childhood and the need for clinical consideration of initiation of preventive cardiology in asymptomatic young adults. Therefore, the aim of the present study is to evaluate the changes in cardiovascular risk factors in asymptomatic individuals followed for 17 years from childhood/adolescence to young adulthood.

Methods

Study population

This prospective cohort study was conducted to examine the evolution of cardiovascular risk factors among young adults followed from age 10–18 years at baseline in 1999 to age 27–36 years in 2016 (17-year follow-up). The base population consisted of children and adolescents living in the municipality of Veranópolis who were regularly enrolled in school in 1999. This municipality is located in Rio Grande do Sul, the southernmost state of Brazil, and in 1999, it had a population of 19,440 inhabitants, of whom 3,438 were aged 10–18 years. Participants were recruited among elementary, middle, and high school students attending local municipal, state-run, or private schools. Baseline exclusion criteria were previous chronic disease (e.g., heart disease, thyroid disease, liver disease, nephropathy, and coagulopathy) or acute disease (e.g., infectious and

contagious diseases), continued use of medication (e.g., oral anticoagulants, contraceptives, and systemic corticosteroids), or pregnancy. A detailed selection of participants for the 1999 cohort has been described in previous studies [11,12]. After the baseline collection in 1999 ($n = 205$), the participants were followed up with two more collections in 2006 ($n = 159$) and 2016 ($n = 156$). Figure 1 provides the flow diagram of participant recruitment and follow-up, with information on losses from 1999 to 2016.

Data collection

Baseline and follow-up evaluations included interviews with the participants (and their parents if minors) using a standardized questionnaire for collection of sociodemographic and behavioral data (sex, age, race, level of education, marital status, income, smoking, physical activity, health status, and medication use), clinical examination, blood collection, and anthropometric measurements. The following variables were assessed: body mass index (BMI); waist circumference (WC); systolic blood pressure (SBP) and diastolic blood pressure (DBP); lipid profile [total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides]; and fasting glucose.

All measurements were made by following the standardized procedures used in the 1999 and 2006 evaluations, as fully described in previous studies [11,13]. Briefly, weight (kg) and height (m) were measured with the participants wearing light clothes and without shoes, and BMI was calculated (kg/m^2). Participants with $\text{BMI} < 25 \text{ kg}/\text{m}^2$ were classified as normal weight. WC was measured at the midpoint between the costal margin and the superior iliac crest, and normal WC was defined as $< 94 \text{ cm}$ in men and $< 80 \text{ cm}$ in women [14]. Blood pressure measurements followed the recommendations of the Second Task Force on Blood Pressure Control in Children in the 1999 evaluation [15] and of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the 2006 evaluation [16]. In all evaluations, blood pressure was measured after a 15-minute rest using a validated sphygmomanometer having an appropriate-size cuff with an inflatable bladder covering 80% of the arm circumference, taking into account the age and body composition of the participant. An electronic sphygmomanometer was used in the 1999 measurements, while manual sphygmomanometers were used in 2006 and 2016. The mean of three measurements was used in the

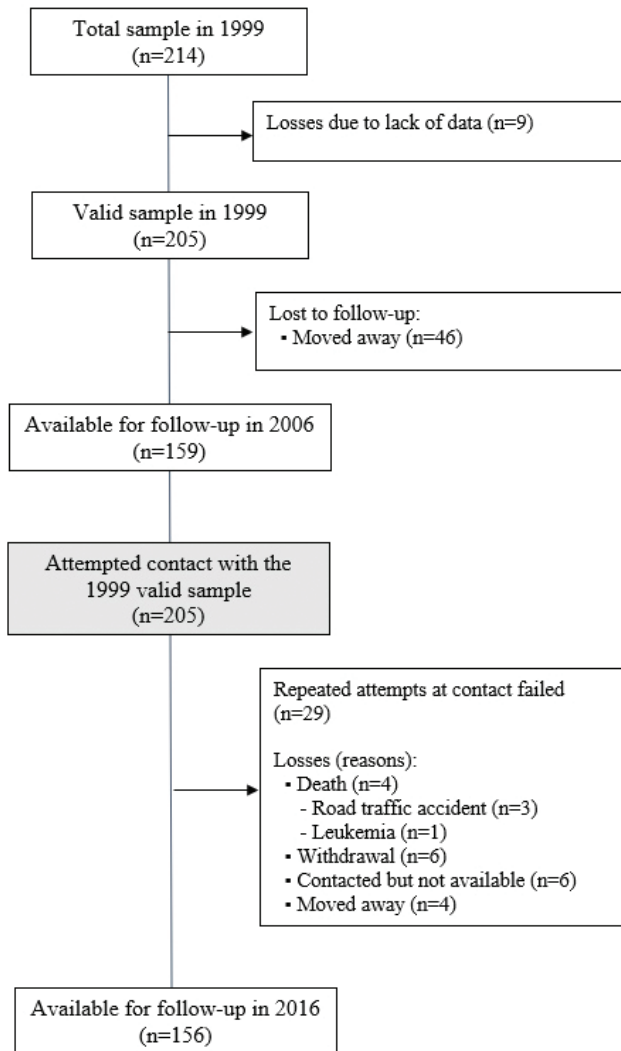


Figure 1. Flow diagram of participant recruitment and follow-up (1999–2016), with information on losses adjusted for the present study.

analysis. Normal blood pressure was defined as SBP ≤ 120 mmHg and DBP ≤ 80 mmHg [17,18]. Blood samples (10 ml) were drawn after a 12-hour fast for determination of lipid profile and fasting glucose. The following levels were defined as normal (reference values for individuals aged >20 years): total cholesterol < 190 mg/dl; HDL-C >40 mg/dl; LDL-C < 130 mg/dl; triglycerides < 150 mg/dl; and fasting glucose < 100 mg/dl [19].

Statistical analysis

Quantitative data are expressed as mean \pm standard error of the mean (SEM). Categorical data are expressed as absolute and relative frequencies. Changes in the variables of interest over time were analyzed using generalized estimating equations (GEEs) with logit link for binary outcomes and independent correlation structure, followed by Bonfer-

roni correction. To investigate the interaction effect between risk factors and sex versus time, a GEE linear regression model was used to analyze quantitative outcomes, while a GEE binary logistic regression model was used for categorical outcomes. All analyses were performed using statistical package for the social sciences, version 21.0, and a $p < 0.05$ was considered significant.

Ethics

The study was approved by the Research Ethics Committee of Universidade do Vale do Rio dos Sinos (UNISINOS; approval number 180/2015) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Results

A total of 156 cohort participants were available for follow-up in 2016, with a mean age of 29.9 ± 0.2 years. The main characteristics of the 2016 participants are shown in Table 1.

Participants' data collected in 1999, 2006, and 2016 were analyzed and compared to determine the evolution of cardiovascular risk factors over time, and the results are shown in Table 2. During follow-up, there were significant increases in BMI, WC, DBP, total cholesterol, triglycerides, and HDL-C ($p < 0.001$). Regarding HDL-C, when only those with HDL-C ≤ 40 mg/dl were analyzed, there was no significant change in HDL-C levels over time ($p = 0.154$).

Significant reductions were observed in SBP, number of individuals with increased blood pressure, physical activity, and fasting glucose ($p < 0.001$). However, when participants with increased fasting glucose were analyzed separately, there was no significant change in glucose levels over time ($p = 0.151$) (Table 2).

As for the interaction between cardiovascular risk factors and sex versus time, male BMI and WC values were significantly higher than those of female participants over time ($p < 0.001$; Fig. 2). Regarding blood pressure, the increase in DBP was significantly greater in men ($p = 0.024$), while the decrease in SBP was significantly greater in women ($p < 0.001$), see Figure 3.

In the analysis of lipid profile, the increase in total cholesterol ($p = 0.032$), LDL-C ($p = 0.002$), and triglyceride levels ($p = 0.011$) was significantly greater in men than in women over time. However, HDL-C levels were significantly higher in women

Table 1. Characteristics of the 2016 cohort participants ($n = 156$).

Variable	Absolute frequency (n)	Relative frequency (%)
Sex		
Male	80	51.3
Female	76	48.7
Marital status		
Married	77	49.4
Separated/divorced	1	0.6
Single	78	50.0
Race		
White	145	92.9
Black	3	1.9
Mixed race	8	5.1
Education		
5–8 years of schooling	3	1.9
9–12 years of schooling	44	28.2
≥ 13 years of schooling	109	69.9
Personal income		
1–5 × minimum wage	128	82.1
6–10 × minimum wage	23	14.7
≥ 10 × minimum wage	5	3.2
Physical activity*		
Yes	78	50.0
No	78	50.0
Smoking		
Non-smoker	131	84.0
Ex-smoker	14	9.0
Smoker	11	7.1
Self-reported health		
Excellent	40	25.6
Very good	48	30.8
Good	62	39.7
Average	6	3.8
Current medication use		
Yes**	80	51.3
No	76	48.7

* Minimum of 45 minutes twice a week.

** Sixty-six women were using oral contraceptives, while the remaining 14 participants were using over-the-counter medicines for the treatment of common disorders (none of them had chronic diseases).

than in men ($p < 0.001$), whose levels remained almost unchanged over time (Fig. 4).

Individual changes from 1999 to 2006 to 2016 across the primary outcomes have been described in a previous publication [12].

Discussion

Identifying cardiovascular risk factors in young adults and determining their evolution over time, as well as the behavior of other associated factors, is an important tool to define actions that can alter the course of risk exposure and prevent the progression of CVD. Over a 17-year period, our cohort of asymptomatic young adults showed (statistically significant) unfavorable changes in cardiovascular risk factors, as assessed at three different time points. An analysis of the interaction between risk factors and sex over time showed significant differences between men and women in all variables of interest, always unfavorable to men.

Hypertension is often associated with metabolic disorders and functional and/or structural changes in target organs, which are aggravated by the presence of other risk factors, such as dyslipidemia and abdominal obesity [18]. In our cohort, the highest levels of SBP were observed in 1999, reducing significantly from 1999 to 2016, especially in women. In the 1999 study, although mean SBP levels were considered clinically altered (mean of 130.6 mmHg) for individuals aged 10–18 years, their mean DBP levels were not altered (65.8 mmHg). Based on that, the authors did not classify these participants as “hypertensive,” stating that individuals with elevated blood pressure should be considered hypertensive only if their blood pressure levels have been constantly above the reference limits after repeated measurements over time—which was not the case, as the participants were subjected to only one session of blood pressure measurement. Also, blood pressure can be highly variable within the same person on the same day, especially in children who may be highly anxious during the assessment. In addition, based on the data from the literature suggesting that the use of electronic devices may increase blood pressure levels [20], in the 1999 study, the authors hypothesized that the use of an electronic rather than a manual sphygmomanometer might have influenced their measurements, thus recommending the use of manual sphygmomanometers for future studies—recommendation that was followed, as manual sphygmomanometers were used in the 2006 and 2016 evaluations. Therefore, considering that no significant difference was observed in SBP levels between 2006 and 2016 and that DBP remained within the normal range over time, it is possible that the 1999–2016 differences are attributable to measurement bias.

Table 2. Changes in anthropometric data, blood pressure levels, and biochemical data from 1999 to 2016 ($n = 156$).

Variables	1999*	2006*	2016	1999–2016 difference (95% CI)	<i>p</i> -value
Age (years), mean \pm SEM	13.2 \pm 0.2	20.7 \pm 0.2	29.9 \pm 0.2	16.7 (16.5–16.9)	-
BMI (kg/m ²), mean \pm SEM	21.4 \pm 0.3 ^a	23.8 \pm 0.3 ^b	26.1 \pm 0.4 ^c	4.7 (3.9–5.5)	< 0.001
BMI \geq 25 kg/m ² , <i>n</i> (%)	31 (18.3) ^a	45 (30.8) ^b	84 (53.8) ^c	36 (26–45)	< 0.001
WC (cm), mean \pm SEM	72.7 \pm 0.8 ^a	76.9 \pm 0.8 ^b	88.4 \pm 0.9 ^c	15.7 (13.7–17.6)	< 0.001
Increased WC (cm), <i>n</i> (%)**	21 (12.4) ^a	21 (14.3) ^a	76 (48.7) ^b	36 (26–46)	< 0.001
TC (mg/dl), mean \pm SEM	177.1 \pm 2.2 ^a	181.4 \pm 2.8 ^a	189.9 \pm 2.9 ^b	12.8 (5.8–19.7)	< 0.001
TC \geq 190 mg/dl, <i>n</i> (%)	55 (31.3) ^a	59 (39.3) ^{ab}	67 (42.9) ^b	12 (1–22)	0.026
HDL-C (mg/dl), mean \pm SEM	46.4 \pm 0.6 ^a	53.3 \pm 0.8 ^b	54.7 \pm 1.2 ^b	8.3 (5.7–10.9)	< 0.001
HDL-C \leq 40 mg/dl, <i>n</i> (%)	31 (17.6)	17 (11.3)	24 (15.4)	-2 (-11 to 6)	0.154
LDL-C (mg/dl), mean \pm SEM	113.2 \pm 1.9	109.5 \pm 2.6	114.7 \pm 2.4	1.5 (-4.4 to 7.4)	0.155
LDL-C \geq 130 mg/dl, <i>n</i> (%)	42 (23.9)	37 (24.7)	45 (28.8)	5 (-5 to 15)	0.482
TG (mg/dl), mean \pm SEM	87.6 \pm 3.2 ^a	89.6 \pm 3.4 ^a	102.2 \pm 4.5 ^b	14.7 (2.7–26.6)	0.011
TG \geq 150 mg/dl, <i>n</i> (%)	14 (8.0) ^a	16 (10.7) ^{ab}	26 (16.7) ^b	9 (0–17)	0.042
SBP (mmHg), mean \pm SEM	130.6 \pm 1.4 ^b	118.6 \pm 1.1 ^a	119.9 \pm 1.1 ^a	-10.7 (-14.1 to -7.2)	< 0.001
DBP (mmHg), mean \pm SEM	65.8 \pm 0.8 ^a	71.6 \pm 1.0 ^b	74.9 \pm 0.7 ^c	9.1 (6.8–11.4)	< 0.001
Increased BP (mmHg), <i>n</i> (%)***	118 (69.4) ^b	64 (43.5) ^a	73 (46.8) ^a	-23 (-33 to -12)	< 0.001
GLY (mg/dl), mean \pm SEM	87.2 \pm 0.7 ^b	87.9 \pm 1.4 ^b	84.3 \pm 0.7 ^a	-2.9 (-4.8 to -1.0)	0.001
GLY \geq 100 mg/dl, <i>n</i> (%)	14 (8.0)	10 (6.7)	6 (3.8)	-4 (-10 to 1)	0.151
Physically active, <i>n</i> (%)	144 (84.7) ^b	58 (39.2) ^a	78 (50) ^a	-35 (-46 to -24)	< 0.001

95% CI = 95% confidence interval; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; GLY = fasting glycemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; SEM = standard error of the mean; TC = total cholesterol; TG = triglycerides; WC = waist circumference.

* In some parameters, the number of participants does not add up to the same total because of missing values.

** Normal WC was defined as < 94 cm in men and < 80 cm in women.

*** Normal BP was defined as SBP \leq 120 mmHg and DBP \leq 80 mmHg.

Different superscript lowercase letters (^{a,b,c}) within the same row indicate significant differences (Bonferroni *post hoc* test, $p < 0.05$).

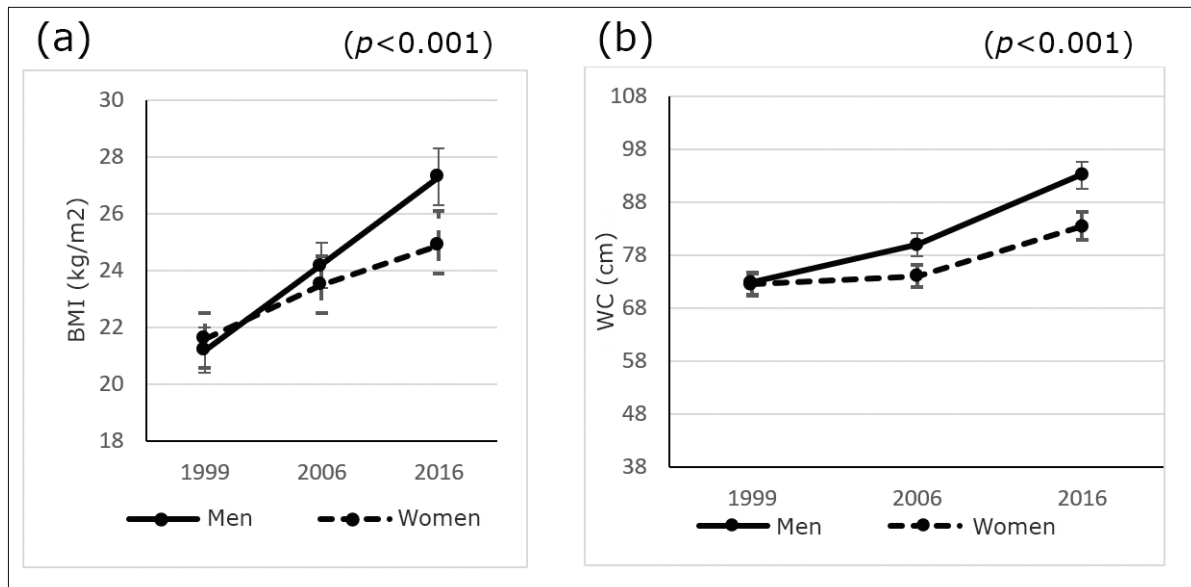


Figure 2. Changes in (a) BMI and (b) WC over time according to sex ($n = 156$). Results are shown as mean \pm SEM. Differences between men and women were determined using a GEEs model.

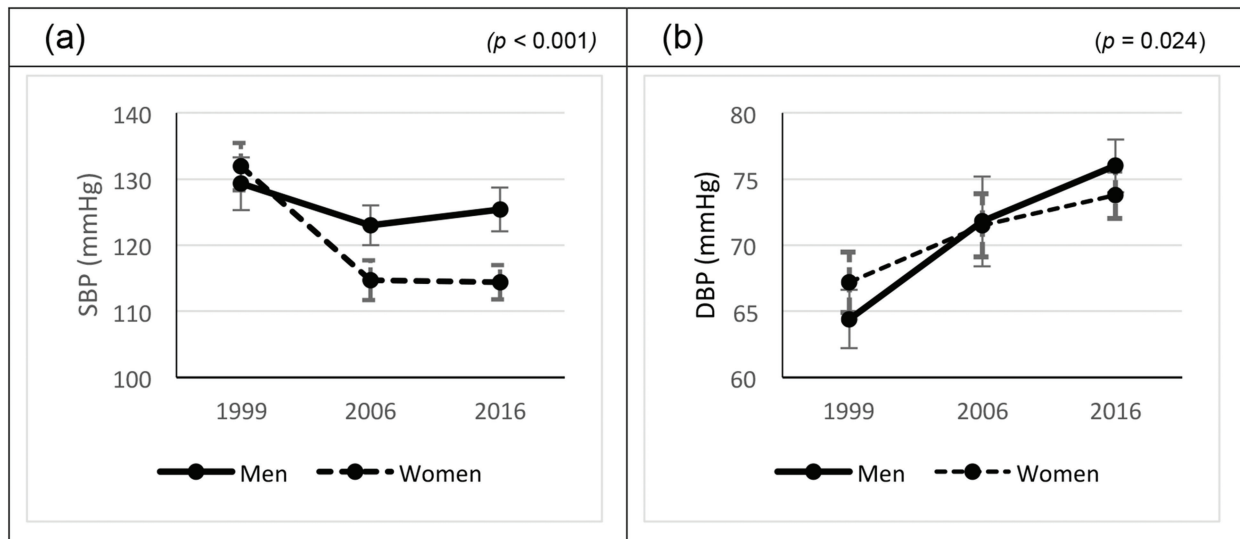


Figure 3. Changes in (a) SBP and (b) DBP over time according to sex ($n = 156$). Results are shown as mean \pm SEM. Differences between men and women were determined using a GEEs model.

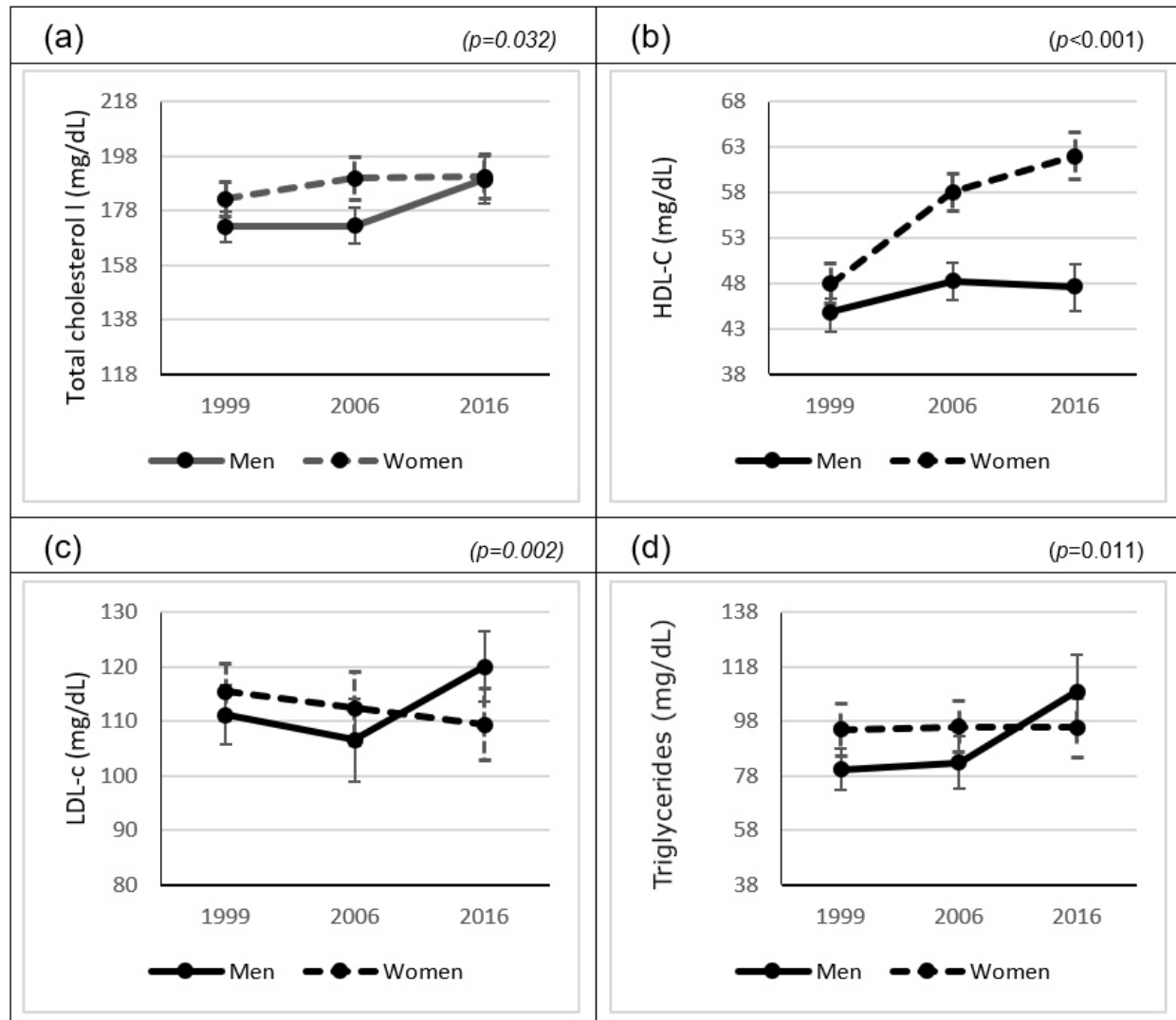


Figure 4. Changes in (a) total cholesterol, (b) HDL-C, (c) LDL-C, and (d) triglycerides over time according to sex ($n = 156$). Results are shown as mean \pm SEM. Differences between men and women were determined using a GEEs model.

Regarding lipid profile, men had a greater increase in the levels of total cholesterol, LDL-C, and triglycerides from 2006 to 2016 than women. HDL-C levels, however, increased significantly over time in women, but remained almost unchanged in men. Total cholesterol and triglyceride levels remained stable from 1999 to 2006, showing significant variation only when compared with the 2016 levels. The significantly increased HDL-C levels observed in women in our study are encouraging, as increased HDL-C is associated with reduced risk of CVD. Consistent with our results, data from the Framingham study show that the relative risk of developing coronary artery disease decreases from 4 to 1 when HDL-C increases from 15 to 45 mg/dl [21]. However, the increased HDL-C and decreased LDL-C levels observed in women may be associated with the use of oral contraceptives reported by the female participants when asked about current medication use. In a study of 1541 women aged 35–55 years, longer duration of oral contraceptive use was positively associated with increasing HDL-C levels and decreasing LDL-C levels [22].

This study has some limitations. The original 1999 study had a cross-sectional design, and its sample size was calculated (and was statistically adequate) to obtain a representative sample of the population aged 10–18 years to describe the prevalence of cardiovascular risk factors among children and adolescents in the municipality of Veranópolis. However, when a cross-sectional study is repeated and the same sample is studied for a second time or a third time, as in the present study, the original cross-sectional study will become a cohort study. Therefore, by being a cohort study, a limitation of this study is that the sample size was not planned to monitor trends in cardiovascular risk factors in these children and adolescents over time. For the present study, using WinPEPI, version 11.43, we calculated that we would need a sample size of 176 individuals to give 95% power to detect changes in cardiovascular risk factors over time (with a 5% significance level), given an anticipated dropout rate of 20%. In this respect, a limitation inherent in this type of study is the difficulty in contacting the participants from the original cohort and recruiting them for the present investigation. In a previous study, in the same cohort aiming to associate coronary artery calcium scores with the evolution of cardiovascular risk factors, it was calculated that a sample size of 154 individuals could give 90% power to detect a difference of 25% in the reduc-

tion in HDL-C levels between groups [12]. Since we were able to recruit 156 participants, the present study was powered enough to observe significant differences, thereby not altering the interpretation of the present results.

In conclusion, the changes in cardiovascular risk factors observed in the present study confirm previous observations in the literature that these changes have important implications for the future progression of CVD. The unfavorable evolution of cardiovascular risk factors assessed in our cohort from 1999 to 2016 shows a trend toward worsening of these risk factors from childhood/adolescence to adulthood. This finding should serve as a warning to public health officials of the need for health promotion strategies aimed at beginning preventive measures in childhood and adolescence. These include screening, health education, mass-media information, and support for primary healthcare. This finding may also foster further research aiming to develop protocols for studying young populations with low HDL-C levels associated with other cardiovascular risk factors, in an attempt to provide a basis for developing practical recommendations that may have some clinical application in decelerating the process of CVD progression.

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Authors' Contributions

Sadi Poletto and Emilio Moriguchi contributed to the conception or design of the work. Sadi Poletto and Neide Maria Bruscato were responsible for contacting and recruiting participants. Neide Maria Bruscato, Manoel Luiz S Pitrez Filho, Luiz Telmo R Vargas, João Carlos B Santana, and Jorge Antônio Hauschild contributed to the acquisition, analysis, or interpretation of data for the work. Sadi Poletto drafted the manuscript. Emilio Moriguchi critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest

The authors declare that there is no conflict of interest.

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