Original Article

Role of Menopause on Cardiometabolic Profile and Lipoprotein Subfractions: Results from the SHIP-Brazil Study

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Abstract

Background: **Menopause is characterized by reduced estrogen production and has been associated with increased cardiovascular disease (CVD) risk.**

Objectives: **To evaluate the influence of menopause on the lipid profile and subfractions of atherogenic lipoproteins associated with cardiovascular risk.**

Methods: **Socioeconomic, anthropometric, clinical, and laboratory data were collected. Glucose was measured using a commercial kit; total cholesterol (TC), triglycerides (TG), and HDL-c were analyzed semi-automatically, and LDL-c was calculated using a standard equation. LDL and HDL subfractions were assessed using the Lipoprint Electrophoresis System. Cardiovascular risk was estimated using the PREVENT calculator. Statistical analyses were performed adopting a significance level of $p < 0.05$.**

Results: **Among 241 women, 133 (55.2%) were postmenopausal. In the fully adjusted model, menopausal status was associated with cardiovascular risk score ($\beta = 0.813$; $p < 0.001$), TC ($\beta = 0.013$; $p < 0.001$), and LDL-c ($\beta = 0.031$; $p < 0.001$) concentrations; and was inversely associated with BMI ($\beta = -0.019$; $p < 0.001$), waist circumference ($\beta = -0.005$; $p = 0.029$), DBP ($\beta = -0.005$; $p = 0.026$), and TG ($\beta = -0.079$; $p < 0.001$). Regarding lipoprotein subfractions, menopausal status was associated with large HDL ($\beta = 0.076$; $p < 0.001$), intermediate HDL ($\beta = 0.020$; $p = 0.005$), small HDL particles ($\beta = 0.035$; $p < 0.001$), small LDL particles ($\beta = -0.140$; $p < 0.001$), and the large-to-small LDL ratio ($\beta = 0.130$; $p < 0.001$).**

Conclusions: **Menopausal status remained associated with higher global cardiovascular risk and significant qualitative remodeling of lipoprotein subfractions.**

Keywords: **Menopause; Cardiovascular Diseases; Atherosclerosis; Public Health; Women's Health.**

Introduction

Cardiovascular diseases (CVDs) are well established as the leading cause of morbidity and mortality worldwide.[1] Atherogenic dyslipidemia is a major contributor to this burden and is characterized by low concentrations of high-density lipoprotein cholesterol (HDL-c), elevated triglycerides (TG), and increased levels of small, dense low-density lipoprotein cholesterol (LDL-c).[2] Literature reviews indicate that women experience a protective hormonal effect against CVDs, largely due to higher estrogen levels compared with men.[1-5]

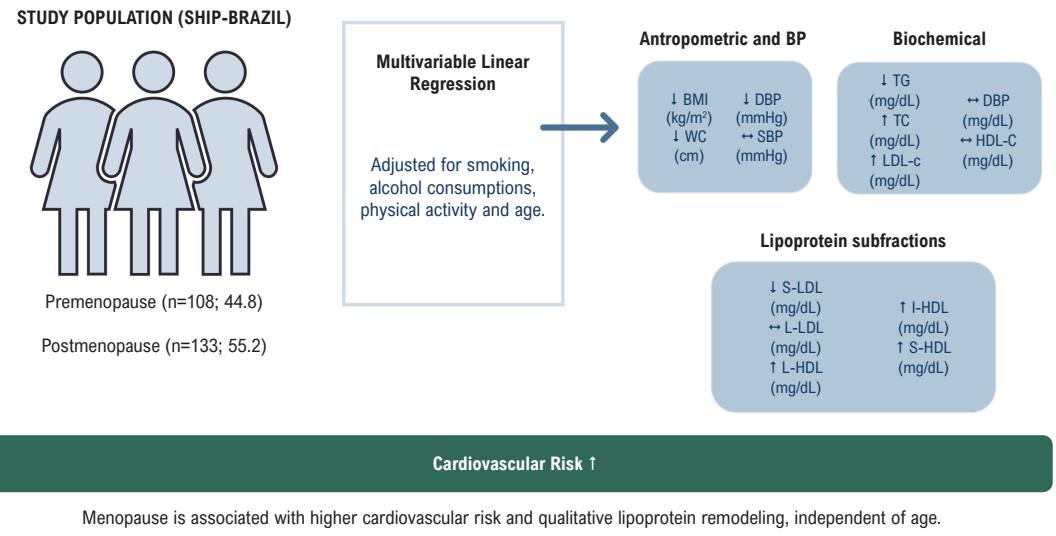
As the biological course of life progresses, the physiological cardiovascular protection observed in women declines during the menopausal transition, typically occurring between 48 and 50 years of age. This period is marked by 12 months of amenorrhea and classic symptoms such as hot flashes, night sweats, mood changes, and vaginal dryness.[5] Among these changes, the exponential decline in estrogen leads to a reduction in the protective cardiovascular effects seen during premenopause. Consequently, lower estrogen levels contribute to an increased likelihood of cardiovascular events in women.[6,7]

In addition to quantitative lipid changes, the menopausal transition brings significant qualitative alterations in lipoproteins

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Central Illustration: Role of Menopause on Cardiometabolic Profile and Lipoprotein Subfractions: Results from the SHIP-Brazil Study



Menopause is associated with higher cardiovascular risk and qualitative lipoprotein remodeling, independent of age.

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that can increase CVD risk. Lower estrogen levels are associated with a more atherogenic lipoprotein profile, characterized by a higher concentration of triglyceride-rich lipoproteins, reduced HDL functionality, and a greater proportion of small, dense LDL particles, which are more prone to oxidation and endothelial penetration, regardless of total LDL cholesterol levels.[8] International studies show that these changes in lipoprotein subfractions begin during menopause and become more pronounced thereafter.[9,10]

In Brazil, population-based data on menopause-related changes in lipoprotein subfractions remain limited. Studies integrating menopausal status with detailed lipoprotein phenotyping are particularly scarce.[11,12] This gap is even more evident in southern Brazil, where cardiometabolic risk factors are highly prevalent and regional analyses of menopause and atherogenic lipoprotein subfractions are few.

There is a clear need for further research on chronic noncommunicable diseases (NCDs), such as CVDs, which are largely driven by atherogenic dyslipidemia in postmenopausal women. This need is reinforced by the scarcity of studies conducted in southern Brazil.[13] The aim of the present study was to evaluate the influence of menopause on the lipid profile and subfractions of atherogenic lipoproteins associated with cardiovascular risk.

Methods

Study design

This cross-sectional, population-based study was conducted in Pomerode, Santa Catarina, Brazil, between 2014 and 2018. Participant selection was performed using simple random sampling, organized into 12 strata according to sex and age group (20-79 years, in 10-year intervals). The initial sample size calculation estimated 3,678 individuals; however, after losses and refusals, the final study population comprised 2,488 participants.[14]

The study was approved by the Human Research Ethics Committee under Ethical Review Submission Certificate No. 884946624.6.0000.5370. Inclusion criteria required participants to have resided in Pomerode for at least six months and to fall within the established age range. Exclusion criteria included cognitive or communication limitations that could hinder questionnaire administration.[14]

For the present analysis, a subsample of women was selected, including those who completed the women's health questionnaire and had biological data available, resulting in a final analytical sample of 241 participants (Figure 1).

Assessment of the sociodemographic profile and menopause status

Questionnaires were administered to collect information on sociodemographic characteristics, including age, sex, women's health, smoking status, physical activity, alcohol consumption, medication use, and self-reported medical diagnoses. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) and categorized according to established guidelines.[14] Alcohol consumption was evaluated using the Alcohol Use Disorders Identification Test (AUDIT) and classified as low risk or moderate/high/severe risk.[14] Type 2 diabetes mellitus (DM2), systemic arterial hypertension, and dyslipidemia were defined based on self-reported previous medical diagnoses.[14] Information on lipid-lowering medication use and history of hormone replacement therapy was obtained through self-report.[14] Hormone replacement therapy was assessed with the question: "Have you ever undergone hormone replacement therapy?" and categorized as 'yes' or 'no'.

To analyze women's menopausal status, a proxy variable was created according to the 2024 Brazilian Guideline on Cardiovascular Health in Climacteric and Menopause.[7] Menopause was defined as the absence of menstruation for 12 months or more, including women who had undergone hysterectomy and/or oophorectomy.

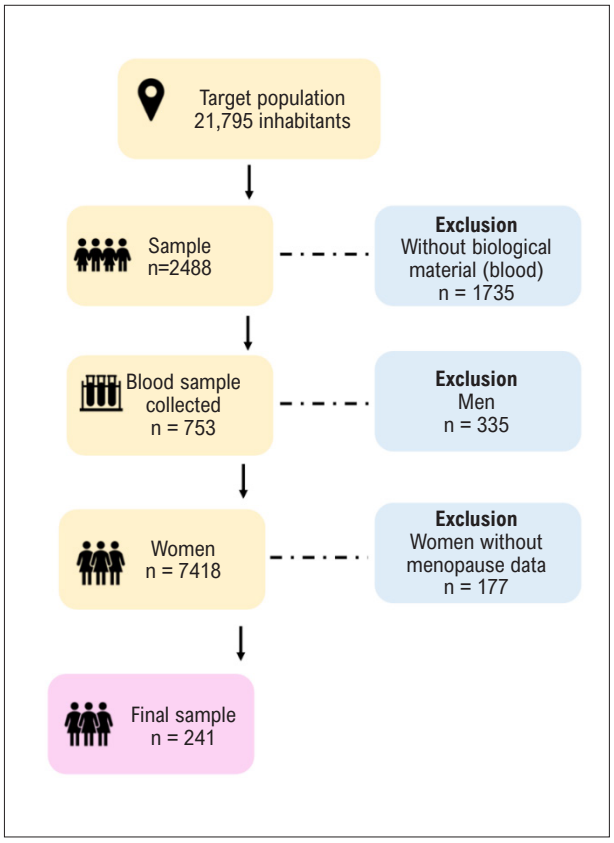


Figure 1 – *Flowchart illustrating the participant selection process.*

Anthropometric assessment

Height and weight were measured to calculate and classify BMI according to WHO criteria for adults[15] and Pan American Health Organization criteria for older adults.16 Waist circumference (WC) was measured midway between the lowest rib and the right superior iliac crest when no visibly narrow point was present. WC was then classified according to WHO cutoff points.[17]

Biochemical analysis

Total cholesterol (TC), TG, and HDL-c concentrations were measured in plasma using the semi-automated Cobas Mira system, and LDL-c was calculated using the formula proposed by Friedewald et al.[18] The TG/HDL-c, TC/HDL-c, and LDL-c/HDL-c ratios were also computed. LDL and HDL subfractions were determined using the Lipoprint® system (Quantimetrix Inc., Redondo Beach, CA, USA), a non-denaturing polyacrylamide gel electrophoresis method that separates lipoprotein particles by size.

HDL particles were classified into 10 subfractions (HDL-1 to HDL-10), ranging from the largest and least dense (HDL-1) to the smallest and densest (HDL-10). These subfractions were grouped as large HDL (HDL-1 to HDL-3), intermediate HDL (HDL-4 to HDL-7), and small HDL (HDL-8 to HDL-10). LDL particles were separated into seven subfractions (LDL-1 to LDL-7), with LDL-1 and LDL-2 representing large LDL particles, and LDL-3 to LDL-7 representing small, dense LDL particles. The large-to-small HDL ratio [(HDL-1 + HDL-2)/(HDL-9 + HDL-10)] and the large-to-small LDL ratio [(LDL-1 + LDL-2)/(LDL-3 to LDL-7)] were also calculated.

Plasma glucose levels were measured according to the manufacturer's instructions using the commercial enzymatic and colorimetric Glucose PAP Liquiform® kit.

Cardiovascular risk estimation

Cardiovascular risk was estimated using the Prediction of Risk of Cardiovascular Events (PREVENT) equations to calculate the 10-year risk of atherosclerotic cardiovascular disease (ASCVD). The PREVENT equations incorporate age (30–79 years), sex, TC, HDL-c, systolic blood pressure (SBP), use of antihypertensive medication, use of statins, DM2, smoking status, BMI, and estimated glomerular filtration rate (eGFR). eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on serum creatinine, age, and sex, excluding race.[19,20]

Statistical analysis

All statistical analyses were conducted using sample weights to minimize potential selection bias and preserve population representativeness. Sample weights were derived using a two-stage inverse probability weighting approach. The first stage accounted for the probability of selection into the study sample, whereas the second stage accounted for the probability of inclusion in the analytical subsample. The final weights were incorporated into all descriptive and regression analyses.[14]

Descriptive statistics were performed, with continuous variables expressed as means and standard deviations or medians and interquartile ranges, according to their distribution; categorical variables were expressed as absolute frequencies (n) and percentages (%). Data normality was assessed using the Kolmogorov–Smirnov test. To compare means between two groups, the independent-samples t-test was used for parametric data, and the Mann–Whitney test was used for non-parametric data. Associations between categorical variables were evaluated using the chi-square test (χ^2). Analyses were performed using available data for each variable; therefore, the number of observations may vary slightly across variables due to missing data.

A multiple linear regression model was used to assess the association between menopause (exposure variable) and cardiometabolic outcomes, including blood pressure, anthropometric measurements, lipid profile, glycemia, and HDL and LDL fractions. Multicollinearity was evaluated using variance inflation factors (VIFs), tolerance values, and condition indices. All predictors showed low VIF values (< 3) and condition indices below 15, indicating no evidence of multicollinearity. Variables with asymmetric distributions were log-transformed before regression analyses, when necessary, to improve compliance with normality and homoscedasticity assumptions.

A hierarchical adjustment strategy was adopted, with age included in the final model because it is an important potential confounder of the association between menopausal status and cardiometabolic outcomes. This approach allowed us to determine whether the observed associations persisted after adjusting for chronological aging. Three models were used: Model 1, unadjusted; Model 2, adjusted for smoking, alcohol consumption, and physical activity; and Model 3, adjusted for smoking, alcohol consumption, physical activity, and age. All analyses were performed using SPSS statistical software version 22.0, adopting a significance level of 5% ($p < 0.05$).

Results

Of the 241 women included in the study, 133 (55.2%) were postmenopausal and 108 (44.8%) were premenopausal. Table 1 presents the demographic, clinical, and biochemical parameters stratified by menopausal status.

Table 1 – Demographic, clinical, and biochemical parameters of female participants

Variables	Total (n=241)	Pre-menopause (n=108)	Post-menopause (n=133)	p-value
Age (years)	44 (15)	36 (9)	58 (11)	<0.001
BMI (kg/m²)	27.70 (24.01 – 32.74)	26.45 (23.18 – 31.29)	29.75 (25.79 – 34.15)	<0.001
WC (cm)	84 (74 - 95)	80.30 (71 – 90.80)	90 (82.80 - 98)	<0.001
SBP (mmHg)	115.50 (108 – 125)	113.50 (104 – 122.50)	123 (113.50 - 132.50)	<0.001
DBP (mmHg)	73 (66.50 – 79.50)	72 (65.50 – 78.50)	74 (70 – 80.50)	<0.001
ASCVD Risk Prevent (%)	0.82 (0.30 - 2.33)	0.40 (0.24 - 0.77	3.65 (1.68 - 6.96)	<0.001
Physical inactivity, n/N (%)	166/223 (74.4)	73/103 (70.9)	93/120 (77.5)	<0.001
Alcohol consumption, n/N (%)	41/235 (17.4)	30/106 (28.3)	11/129 (8.5)	<0.001
Smoking, n/N (%)			0.027	0,027
Never smoker	179/236 (75.8)	80/106 (75.5)	99/130 (76.2)	
Former smoker	43/236 (18.2)	19/106 (17.9)	24/130 (18.5)	
Current smoker	14/236 (5.9)	7/106 (6.6)	7/130 (5.4)	
Hypertension, n/N (%)	79/216 (36.6)	18/96 (18.8)	61/120 (50.8)	<0.001
Dyslipidemia, n/N (%)	68/232 (29.3)	10/104 (9.6)	58/127 (45.7)	<0.001
T2DM, n/N (%)	23/238 (9.7)	1/108 (0.9)	22/130 (16.9)	<0.001
Lipid-lowering, n/N (%)	6/161 (3.7)	0/60 (0.0)	6/101 (5.9)	0.058
History of HRT, n/N (%)	29/189 (15.3)	12/87 (13.8)	17/102 (16.7)	
Biochemical Variables				
Glucose (mg/dL)	88 (73 - 107)	85 (71 - 97)	99 (77 - 118)	<0.001
TG (mg/dL)	106 (77 - 147)	97 (69 - 127)	106 (78 - 146)	<0.001
TC (mg/dL)	175 (155 - 197)	172 (153 - 193)	182 (157 - 207)	<0.001
LDL-c (mg/dL)	113.20 (92.40 - 140)	106.20 (88.20 - 124)	113.80 (94 - 139.60)	<0.001
HDL-c (mg/dL)	42 (36 - 53)	44 (37 - 54)	41 (35 - 49)	<0.001
TC/HDL-c	4.04 (3.29 – 4.81)	3.78 (3.11 – 4.56)	4.51 (3.75 – 5.28)	<0.001
LDL-c/HDL-c	2.46 (1.99 – 3.18)	2.32 (1.79 – 2.95)	2.93 (2.28 – 3.40)	<0.001
TG/HDL-c	2.53 (1.70 - 4.01)	2.02 (1.35 - 3.08)	2.66 (1.63 - 3.86)	<0.001

Data are presented as mean (SD), median (IQR), or n/N (%). Percentages were calculated using the number of participants with available data for each variable. Differences between groups were tested using the Chi-square test for categorical variables; an independent-samples t-test or a Mann-Whitney test, depending on the distribution. The significance level was set at p<0.05; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; T2DM: type 2 diabetes mellitus; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; TG: triglycerides; HRT: Hormone replacement therapy.

Regarding HDL and LDL subfractions, the analysis revealed significant differences between pre- and postmenopausal women (Table 2). Overall, postmenopausal women exhibited a more atherogenic lipoprotein profile, characterized by lower concentrations of HDL subfractions – including large, intermediate, and small HDL particles. Furthermore, postmenopausal women showed a lower large-to-small HDL particle ratio, indicating a less favorable HDL profile. Although postmenopausal women also presented higher concentrations of large LDL particles compared with premenopausal women, the ratio of large to small LDL particles was lower in postmenopausal women.

Table 3 presents the associations between menopausal status and cardiovascular risk factors across three hierarchical regression models. In the fully adjusted model (Model 3), menopause was inversely associated with BMI, WC, and DBP, but not with SBP. The associations with glucose and HDL-c were not significant, whereas menopause remained independently associated with higher TC and LDL-c levels. In contrast, TG levels showed an inverse association with menopausal status.

Menopausal status was positively associated with large HDL, intermediate HDL, and small HDL particles. No significant association was observed for the large-to-small HDL ratio after full adjustment. Regarding LDL subfractions, menopausal status was inversely associated with small LDL particles and positively associated with the large-to-small LDL ratio, while no significant association was found for large LDL particles (Central Illustration).

Table 2 – HDL and LDL subfractions of female participants in the SHIP-Brazil study

Variables	Total (n=241)	Pre-menopause (n=108)	Post-Menopause (n=133)	p-value
HDL 1 (mg/dL)	4.27 (2.33)	4.72 (2.46)	3.64 (1.97)	<0.001
HDL 2 (mg/dL)	5.29 (2.56)	5.84 (2.73)	4.5 (2.04)	<0.001
HDL 3 (mg/dL)	3.32 (1.59)	3.66 (1.70)	2.84 (1.3)	<0.001
HDL 4 (mg/dL)	4.34 (2.48)	4.80 (2.93)	3.7 (1.37)	<0.001
HDL 5 (mg/dL)	4.40 (1.55)	4.64 (1.79)	4.06 (1.00)	<0.001
HDL 6 (mg/dL)	7.60 (1.67)	7.82 (1.55)	7.3 (1.8)	<0.001
HDL 7 (mg/dL)	2.85 (0.64)	2.82 (0.61)	2.9 (0.7)	0.168
HDL 8 (mg/dL)	3.45 (0.84)	3.51 (0.90)	3.38 (0.73)	0.007
HDL 9 (mg/dL)	2.86 (0.85)	2.89 (0.91)	2.82 (0.75)	0.963
HDL 10 (mg/dL)	5.38 (2.42)	5.42 (2.55)	5.33 (2.22)	0.216
Large HDL (mg/dL)	12 (8 - 17)	13 (9 – 18)	10 (7 - 13)	<0.001
Intermediate HDL (mg/dL)	19 (16 - 21)	20 (16 - 23)	17.87 (14 - 20)	<0.001
Small HDL (mg/dL)	11 (10 - 14)	11 (10 - 14)	11 (10 - 13)	0.009
HDL Large/HDL Small	1 (1 – 1.54)	1 (0.81 – 1.72)	1 (0.68 – 1.36)	<0.001
LDL 1 (mg/dL)	18.13 (8.44)	17.87 (8.68)	18.53 (8.08)	<0.001
LDL 2 (mg/dL)	12.05 (6.41)	11.17 (6.53)	13.37 (6.0)	<0.001
LDL 3 (mg/dL)	4 (2 - 6)	4 (3 - 8)	3 (2 - 7)	<0.001
LDL 4 (mg/dL)	1 (0 - 2)	0 (0 - 2)	0 (0 - 2)	0.769
LDL 5 (mg/dL)	0.33 (1.25)	0.42 (1.40)	0.20 (1.0)	0.001
LDL 6 (mg/dL)	0.54 (0.34)	0.06 (0.34)	0.04 (0.35)	0.012
LDL 7 (mg/dL)	0.07 (0.37)	0.06 (0.34)	0.09 (0.41)	0.081
Large LDL (mg/dL)	28 (20 - 35)	25 (20 - 33)	31 (26 - 40)	<0.001
Small LDL (mg/dL)	5 (3 - 9)	4 (2 - 6)	4 (2 - 8)	0.001
Large LDL/LDL Small	6 (3.75 – 11.83)	5.89 (4.67 – 13.1)	5.84 (3.21 – 11.87)	0.001

Data are presented as mean (SD) or median (IQR). Differences between groups were tested using the independent-samples t-test or the Mann-Whitney test, depending on the distribution. The significance level was set at p<0.05. Abbreviations: HDL, high-density lipoprotein cholesterol; Large HDL, large HDL subfraction (HDL-1 to HDL-3); Intermediate HDL, intermediate HDL subfraction (HDL-4 to HDL-7); Small HDL, small HDL subfraction (HDL-8 to HDL-10); LDL-c, low-density lipoprotein cholesterol; Large LDL, large LDL subfraction (LDL-1 and LDL-2); Small LDL, small dense LDL subfractions (LDL-3 to LDL-7).

Discussion

The present study provides specific evidence that the cardiometabolic vulnerability observed after menopause is primarily driven by qualitative alterations in lipid metabolism rather than by increases in body mass or central adiposity among Brazilian women. Although postmenopausal women exhibited higher BMI, WC, and blood pressure in the unadjusted analyses, these associations were substantially attenuated after adjustment for age. In contrast, menopausal status remained independently associated with higher cardiovascular risk scores and marked changes in lipoprotein composition.

As highlighted by the WHO, an epidemiological transition is underway in which communicable diseases have been declining in prevalence, while chronic noncommunicable diseases have emerged as the leading causes of mortality in contemporary populations. Within this context, CVDs occupy a prominent position, largely driven by metabolic factors such as dyslipidemia. This condition – characterized by low HDL-c levels, hypertriglyceridemia, and an increase in small, dense LDL particles – is one of the main pathophysiological mechanisms underlying the development and progression of CVD.[21]

The results of this study reinforce that the hormonal transition experienced by menopausal women contributes to a more atherogenic and pro-CVD environment than that observed in premenopausal women.[22] The findings align with previous evidence showing that reduced estrogen levels compromise cardiovascular protection,[1,3] resulting in worsening indicators such as BMI, WC, DBP, cardiovascular risk, TG, TC, LDL-c, and HDL-c.

Poehlman and Tchernof[23] reported that weight gain and increased central fat distribution occur during the first years after menopause. Moreover, the reduction in metabolic energy expenditure during menopause is believed to be one of the key mechanisms promoting

Table 3 – Association between menopause and cardiovascular risk factors

Variables	Model 1 β (95% IC)	p-value	Model 2 β (95% IC)	p-value	Model 3 β (95% IC)	p-value
BMI (kg/m²)	0.043 (0.039; 0.048)	<0.001	0.030 (0.025; 0.035)	<0.001	-0.019 (-0.026; -0.013)	<0,001
WC (cm)	0.046 (0.041; 0.048)	<0.001	0.037 (0.034; 0.041)	<0.001	-0.005 (-0.010; -0.001)	0.029
SBP (mmHg)	0.036 (0.034; 0.039)	<0.001	0.032 (0.029; 0.034)	<0.001	-0.001 (-0.004; 0.003)	0.711
DBP (mmHg)	0.017 (0.014; 0.020)	<0.001	0.015 (0.012; 0.018)	<0.001	-0.005 (-0.009; -0.001)	0.026
ASCVD Risk Prevent (%)*	0.843 (0.815; 0.870)	<0.001	0.813 (0.785; 0.841)	<0.001	-	-
Biochemical Variables						
Glucose (mg/dL)	0.062 (0.057; 0.068)	<0.001	0.066 (0.060; 0.072)	<0.001	0.005 (-0.004; 0.014)	0.245
TG (mg/dL)	0.050 (0.040; 0.060)	<0.001	0.045 (0.035; 0.056)	<0.001	-0.079 (-0.094; -0.064)	<0.001
TC (mg/dL)	0.024 (0.020; 0.029)	<0.001	0.035 (0.030; 0.039)	<0.001	0.013 (0.007; 0.020)	<0.001
LDL-c (mg/dL)	0.038 (0.032; 0.045)	<0.001	0.054 (0.047; 0.061)	<0.001	0.031 (0.021; 0.041)	<0.001
HDL-c (mg/dL)	-0.031 (-0.037; -0.026)	<0.001	-0.024 (-0.030; -0.018)	<0.001	0.003 (-0.006; 0.012)	0.469
Subfractions						
Large HDL (mg/dL)	-0.097 (-0.114; -0.080)	<0.001	-0.046 (-0.064; -0.027)	<0.001	0.076 (0.051; 0.101)	<0.001
Intermediate HDL (mg/dL)	-0.049 (-0.059; -0.040)	<0.001	-0.008 (-0.018; 0.002)	0.108	0.020 (0.006; 0.035)	0.005
Small HDL (mg/dL)	-0.225 (-0.541; 0.091)	0.162	0.041 (0.028; 0.054)	<0.001	0.035 (0.017; 0.054)	<0.001
Large HDL/ Small HDL	-0.095 (-0.115; -0.075)	<0.001	-0.084 (-0.106; -0.062)	<0.001	0.039 (-0.009; 0.069)	0.060
Large LDL (mg/dL)	0.058 (0.041; 0.074)	<0.001	0.045 (0.028; 0.063)	<0.001	0.017 (-0.009; 0.042)	0.197
Small LDL (mg/dL)	0.044 (0.008; 0.081)	0.016	-0.019 (-0.057; 0.020)	0.346	-0.140 (-0.198; -0.083)	<0.001
Large LDL/ Small LDL	-0.059 (-0.809; 0.014)	0.225	0.061 (0.021; 0.100)	0.003	0.130 (0.069; 0.190)	<0.001

*Results are presented as unstandardized regression coefficients (B), 95% confidence intervals (95% CI), and p-values. Variables with asymmetric distributions were log-transformed prior to regression analyses. For these variables, regression coefficients should be interpreted as relative differences between groups. Model 1: unadjusted; Model 2: adjusted for smoking, alcohol consumption, and physical activity; Model 3: adjusted for smoking, alcohol consumption, physical activity, and age. *In Model 2 for Cardiovascular Risk, no adjustment was made for smoking status, as this factor is included in the ACC/AHA formula. Furthermore, Model 3 adjusted for age was also not considered for this variable. ASCVD: atherosclerotic cardiovascular*

increased fat mass, with preferential accumulation of visceral adipose tissue. Accordingly, Mao et al.[24] suggested that elevated follicle-stimulating hormone levels after menopause may contribute to weight gain independently of estrogen decline, although the authors emphasized the need for further studies to isolate these effects. Our findings add nuance to this discussion by showing that, after accounting for age, menopausal status is not independently associated with higher BMI or WC, supporting the hypothesis that aging-related metabolic changes play a predominant role.

Regarding blood pressure, Alhawari et al.[25] reported that postmenopausal estrogen loss contributes to cardiovascular risk, demonstrating that women undergoing hormone replacement therapy exhibit better vascular function and lower oxidative stress. In the present study, although higher SBP and DBP levels were observed in unadjusted analyses, only DBP showed a modest association after full adjustment. These findings align with evidence suggesting that the menopausal transition accelerates vascular aging, increasing arterial stiffness and impairing endothelial function – processes strongly influenced by aging itself.[26-28]

Regarding changes in blood glucose, Dugani et al.[29] observed that increased glucose levels during the postmenopausal period are associated with the incidence of type 2 diabetes and insulin resistance, both of which are key determinants of early CVD development. In our study, associations between menopausal status and fasting glucose were evident in models without age adjustment but became nonsignificant after controlling for age, further underscoring the strong influence of chronological aging on glucose metabolism.

With respect to TG and cholesterol, Bittner et al.[30] emphasize that dyslipidemia is an independent predictor of cardiovascular risk and represents a more significant risk factor for women than for men, particularly during the postmenopausal period. Consistent with this evidence, our results showed that menopausal status remained independently associated with higher TC and LDL-c levels after full adjustment, reinforcing the relevance of lipid metabolism alterations in this population. Thus, menopause is associated with substantial changes in lipid metabolism, favoring the occurrence of cardiovascular events among women.[31] Menopausal women experience a considerable increase in LDL-c, which is closely linked to a high risk of carotid plaque formation.[10]

In addition to the well-established deterioration of HDL-mediated cardioprotective mechanisms, the menopausal transition is also characterized by qualitative changes in LDL particles that may further contribute to cardiovascular vulnerability. While LDL-c concentration remains a clinically relevant parameter, accumulating evidence suggests that LDL particle size and distribution provide complementary insights into atherogenic risk, particularly for improving residual risk management in women. Small, dense LDL particles are characterized by reduced affinity for hepatic LDL receptors, prolonged circulation time, and increased susceptibility to oxidative modification, thereby facilitating endothelial penetration and foam cell formation.[32-34]

Population-based investigations have demonstrated that menopausal status is associated with shifts in LDL subfractions that occur independently of chronological aging. Data from the SWAN Heart Study revealed a decline in large LDL particles and a transition toward a more atherogenic LDL profile during the menopausal transition, particularly in late perimenopause and early postmenopause.[35] Consistently, analyses from the ELSA-Brasil cohort identified increases in triglyceride-rich lipoproteins and unfavorable LDL subfraction patterns following menopause, although these associations were partially attenuated after adjustment for age and lifestyle-related variables.[34]

In the present study, alterations in LDL subfractions after menopause were modest and largely dependent on adjustment for age and lifestyle factors. While unadjusted analyses suggested higher concentrations of both large and small LDL particles among postmenopausal women, these associations were substantially attenuated in the fully adjusted model. Notably, menopausal status was inversely associated with small LDL particles and positively associated with the large-to-small LDL ratio, while no independent association was observed for large LDL concentrations. These findings suggest that previously reported increases in LDL-related cardiovascular risk among postmenopausal women may be more closely related to aging and the broader cardiometabolic context than to menopause itself.

The limited availability of national studies integrating menopausal status, LDL subfractions, and social and lifestyle determinants – particularly in Southern Brazil – highlights an important gap in the current literature. Indeed, the clinical relevance of LDL subfraction analysis, beyond the traditional lipid profile, expands the current understanding of CVD risk during the menopausal period. According to Qi et al., menopause modifies the relationship between vascular health measures and lipoprotein subfractions, as evidenced by a positive association between small-medium LDL and carotid intima-media thickness (cIMT).[35] Conversely, a large population-based Brazilian study did not identify dense LDL subfractions as important markers of subclinical atherosclerotic disease, as measured by coronary calcium score in menopausal women.[36] Together, these controversies underscore the need to investigate additional CVD risk factors during menopause.

In contrast, HDL subfractions exhibited consistent and significant remodeling across models. In both unadjusted and lifestyle-adjusted analyses, postmenopausal women showed lower concentrations of large and intermediate HDL particles and a reduced large-to-small HDL ratio, reflecting a less favorable HDL profile. However, after adjustment for age, menopausal status was associated with higher concentrations of HDL particles across all subfractions, accompanied by a shift in their relative distribution. This pattern suggests qualitative remodeling of HDL rather than a simple reduction in cardioprotective particles. Given that large and intermediate HDL particles are closely linked to cholesterol efflux capacity, antioxidant activity, and endothelial protection, changes in the balance among HDL subfractions may have important functional implications, even when HDL particle concentrations are preserved or increased.[9,32] These particles are recognized for their anti-inflammatory, antioxidant, and cholesterol-efflux-promoting properties, which are essential for endothelial protection. Therefore, the reduction of these subfractions implies a disturbance in HDL's functional cardioprotective capacity.[32]

The SWAN study reported reductions in large and intermediate HDL particles, alongside increases in small HDL particles, after menopause,[34] whereas analyses from the ELSA-Brasil cohort did not identify significant changes after adjustment for age and lifestyle factors.[34] Conversely, El Khoudary et al.[37,38] observed increases in large HDL particles among postmenopausal women. Taken together, these discrepancies suggest that menopausal effects on HDL subfractions are highly context-dependent and may be modulated by aging, adiposity, and metabolic health rather than reflecting a uniform pattern of HDL deterioration. Therefore, HDL subfraction measurements add multiple dimensions related to HDL functionality that go beyond the simple cholesterol content of HDL particles. In line with this, a recent study identified the predictive role of HDL subfractions as markers of non-traditional indicators related to dietary lipid content and visceral adipose tissue.[39]

The results of this study should be interpreted with caution. First, this is a cross-sectional study, which does not allow for causal inference. Furthermore, the sample size was reduced due to the unavailability of complete information for classifying menopausal status in all women. To minimize potential selection bias resulting from participant loss and incomplete biological data, all analyses incorporated sample weights derived from a two-stage inverse probability weighting procedure. Additionally, information on hormone replacement therapy was obtained through self-report and did not include details regarding the type, duration, dose, or formulation of treatment (e.g., tibolone), limiting more detailed analyses of its potential effects on lipid parameters.

Despite these limitations, this study makes an important contribution to the current literature on cardiovascular risk in menopausal women. It provides robust information on biochemical parameters involved in cardiovascular health and extends the analysis to qualitative lipoprotein characteristics by assessing LDL and HDL subfractions using a validated method.

Conclusion

Menopausal status was independently associated with higher cardiovascular risk scores, TC, LDL-c, and qualitative alterations in lipoprotein subfractions after adjustment for lifestyle factors and age. Although positive associations with BMI, WC, and blood pressure were observed in unadjusted models, these associations were reversed after age adjustment, indicating that the unfavorable anthropometric and hemodynamic profile observed in postmenopausal women is largely attributable to chronological aging rather than to menopausal status itself.

Author Contributions

Conception and design of the research: Casarotto LRP, Elias MEG, Alvarenga L, Helena ETS, Valente C; Acquisition of data: Alvarenga L, Helena ETS; Analysis and interpretation of the data: Casarotto LRP, Elias MEG, Alvarenga L; Statistical analysis: Alvarenga L; Funding acquisition: Damasceno NRT, Helena ETS; Writing of the manuscript: Casarotto LRP, Elias MEG; Critical revision of the manuscript for intellectual content: Casarotto LRP, Elias MEG, Alvarenga L, Markus MRP, Völzke H, Damasceno NRT, Helena ETS, Valente C.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Regional de Blumenau (FURB) under the protocol number 884946624.6.0000.5370. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT to improve the readability and clarity of the manuscript, under the authors' supervision. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

All datasets supporting the results of this study are available upon request from the corresponding author.

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