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Original article

Association of dyslipidemia with single nucleotide polymorphisms of the cholesteryl ester transfer protein gene and cardiovascular disease risk factors in a highly admixed population

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SUMMARY

Background and aims: Cardiovascular diseases (CVD) are major causes of mortality worldwide, leading to premature deaths, loss of quality of life, and extensive socioeconomic impacts. Alterations in normal plasma lipid concentrations comprise important risk factors associated with CVD due to mechanisms involved in the pathophysiology of atherosclerosis. Genetic markers such as single nucleotide polymorphisms (SNPs) are known to be associated with lipid metabolism, including variants in the cholesteryl ester transfer protein (CETP) gene. Thus, the study's objective was to assess the relationship among lipid profile, socioeconomic and demographic characteristics, health status, inflammatory biomarkers, and CETP genetic variants in individuals living in a highly admixed population.

Methods: The study comprises an analysis of observational cross-sectional data representative at the population level from a highly admixed population, encompassing 901 individuals from three age groups (adolescents, adults, and older adults). Socioeconomic, demographic, health, and lifestyle characteristics were collected using semi-structured questionnaires. In addition, biochemical markers and lipid profiles were obtained from individuals' blood samples. After DNA extraction, genotyping, and quality control according to Affymetrix's guidelines, information on 15 SNPs in the CETP gene was available for 707 individuals. Lipid profile and CVD risk factors were evaluated by principal component analysis (PCA), and associations between lipid traits and those factors were assessed through multiple linear regression and logistic regression.

Results: There were low linear correlations between lipid profile and other individuals' characteristics. Two principal components were responsible for 80.8 % of the total variance, and there were minor differences in lipid profiles among individuals in different age groups. Non-HDL-c, total cholesterol, and LDL-c had the highest loadings in the first PC, and triacylglycerols, VLDL-c and HDL-c were responsible for a major part of the loading in the second PC;, whilst HDL-c and LDL-c/HDL-c ratio were significant in the third PC. In addition, there were minor differences between groups of individuals with or without dyslipidemia regarding inflammatory biomarkers (IL-1β, IL- 6, IL-10, TNF-α, CRP, and MCP-1). Being overweight, insulin resistance, and lifestyle characteristics (calories from solid fat, added sugar, alcohol and sodium, leisure physical activity, and smoking) were strong predictors of lipid traits, especially HDL-c and dyslipidemia ($p < 0.05$). The CETP SNPs rs7499892 and rs12691052, rs291044, and rs80180245 were significantly associated with HDL-c ($p < 0.05$), and their inclusion in the multiple linear regression model increased its accuracy (adjusted R^2 rose from 0.12 to 0.18).

Conclusion: This study identified correlations between lipid traits and other CVD risk factors. In addition, similar lipid and inflammatory profiles across age groups in the population suggested that adolescents might already present a significant risk for developing cardiovascular diseases in the population. The risk can be primarily attributed to decreased HDL-c concentrations, which appear to be influenced by genetic factors, as evidenced by associations between SNPs in the CETP gene and HDL-c concentrations, as well

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as potential gene–diet interactions. Our findings underscore the significant impact of genetic and lifestyle factors on lipid profile within admixed populations in developing countries.

1. Introduction

Cardiovascular diseases (CVD) are major causes of mortality worldwide, leading to premature deaths and loss of quality of life for populations in several countries and imposing substantial socioeconomic burden on individuals, communities, and health systems [1,2]. Dyslipidemias, characterized by alterations in lipid levels, represent risk factors significantly associated with CVD due to their involvement in the pathophysiology of atherosclerosis [3–5], presenting high prevalence in several countries worldwide, particularly in Brazil [5–7].

There is robust evidence on the role of metabolic and genetic risk factors for CVD and dyslipidemia, showing associations between and within these factors and lipid profiles. Several studies identified associations with inflammatory cytokines, chemokines, and other proteins, as well as hundreds to thousands of genetic variants (e.g., single nucleotide polymorphisms (SNPs)) throughout the genome implicated in dyslipidemia and CVD [8–15].

A recent systematic review highlighted genetic–diet interactions of SNPs in the cholesteryl ester transfer protein (CETP) gene, which are related to HDL-c metabolism and might also affect other lipid traits [16,17]. The CETP-mediated exchange of cholesteryl esters and triglycerides between triglycerides-rich lipoproteins (TRLs) and other lipoproteins, such as HDL, can stimulate atherogenic inflammatory cascades, which will ultimately lead to the formation of atherosclerotic plaques [12,18].

Nonetheless, it should be noted that investigations that address gene–environment interactions and the genetic architecture of lipid traits have been mostly conducted in Caucasian populations rather than highly admixed cohorts, like the Brazilian population [16,19].

Although previous Brazilian studies have shown initial insights on the relationship between lipid traits and several cardiometabolic markers, there is absence of comprehensive evidence on the joint effects of lifestyle choices, socioeconomic characteristics, anthropometric measures, biochemical markers, and genetic variants on dyslipidemia [20,21].

Thus, the present study aimed at analyzing the relationship between lipid profile and cardiometabolic risk factors, including SNPs in the CETP gene, metabolic biomarkers, and lifestyle and sociodemographic characteristics, among different age groups of the population living in urban areas of São Paulo municipality, Brazil.

2. Material and methods

2.1. Study design

This observational study consists of a subsample of the Health Survey of São Paulo (ISA-Capital). It is based on analysis of data obtained from the cross-sectional survey "2015 Health Survey of São Paulo with Focus on Nutrition (2015 ISA-Nutrition)", a population-based study aiming at the evaluation of lifestyle-related modifiable factors, biochemical and genetic markers, as well as environmental factors related to the development of cardiometabolic diseases.

The study was approved by the Research Ethics Committees of the School of Public Health, University of São Paulo (# 43838621.7.0000.5421 and # 30848914.7.0000.5421 for the 2015 ISA-Nutrition). Written informed consent was obtained from all participants.

2.2. Population

Individuals included in the present study were interviewed in the household by trained researchers in 2015, using semi-structured questionnaires within the ISA-Nutrition survey to obtain comprehensive information on demographic, socioeconomic, and lifestyle characteristics, health status, and use of health services. Individuals were categorized into three age groups: adolescents (12–19 years old), adults (20–59 years old), and older adults (≥60 years old), being representative at the municipality level.

The initial sample of the survey was selected through a complex probabilistic sampling of residents living in the urban area of São Paulo city. A subsample of 901 participants, distributed in 629 different households, was randomly selected for collection of venous blood samples after 12–14 h of fasting by trained nurses during a second visit to the individuals' households, allowing the assessment of biochemical markers, nutritional status, and genetic biomarkers. The samples were then processed in the Laboratory of Nutritional Genomics and Inflammation of the School of Public Health of the University of São Paulo. Details of the survey sampling procedures and sample characteristics are available in previous studies [22–24].

2.3. Demographic, socioeconomic, and health characteristics

Information from the ISA-Nutrition 2015 dataset was selected to analyze factors associated with dyslipidemia in São Paulo, including demographic, socioeconomic, and lifestyle characteristics and metabolic markers.

A pre-screening science-driven approach was adopted for selection of variables consistently implicated in dyslipidemia phenotypes according to the literature. Health outcomes analyzed in the study were total cholesterol, VLDL-c, LDL-c, HDL-c, HDL-c/LDL-c, non-HDL-c, and triacylglycerols (TGL), which were determined in the serum with Trinder Reaction and Homogeneous Enzymatic Colorimetric Assay (Cobas; Roche Diagnostic GmbH, Mannheim, GW, Germany).

In addition, categorical variables referring to dyslipidemia were created according to the 2017 Brazilian Dyslipidemia Guidelines (adults and older adults) and I Guideline for Atherosclerosis Prevention in Childhood and Adolescence [25,26].

- Low HDL-c is defined as HDL-c < 40 mg/dL for adult and older adult men, <50 mg/dL for adult and older adult women, and <45 mg/dL for adolescents;
- Isolated hypercholesterolemia is defined as LDL-c > 160 mg/dL for adults and older adults and >130 mg/dL for adolescents;
- Isolated hypertriglyceridemia is defined as TGL >150 mg/dL for adults and older adults and >130 mg/dL for adolescents;

- Mixed hyperlipidemia is defined as the presence of hypertriglyceridemia and hypercholesterolemia;
- Any dyslipidemia (DLP) is defined as the presence of any of the aforementioned categories, including the use of hypolipidemic medication.

Biological and metabolic markers potentially associated with lipid traits included the following categories of variables: the inflammatory biomarkers IL-1β, IL- 6, IL-10, TNF-α, CRP, and MCP-1; variables related to glucose metabolism such as the homeostatic model assessment for insulin resistance (HOMA-IR), insulin and fasting blood glucose levels; anthropometric variables (waist circumference and waist circumference/height ratio and body mass index, BMI); and systolic and diastolic blood pressure. HOMA-IR was calculated based on insulin and glucose levels and categorized into presence or absence of insulin resistance, while BMI was based on the measurement of height and weight of individuals and categorized into No Overweight and Overweight according to age group [27].

Other characteristics included in the analysis were.

- Demographic: sex (male or female), age group (adolescent, adult, or older adult), and ethnicity (white or others);
- Socioeconomic: educational attainment and household income per capita;
- Lifestyle: alcohol use (yes or no), use of tobacco (yes or no), diet quality (12 dietary components included in the Revised Brazilian Healthy Eating Index, BHEI-R), and engagement in global and leisure-time physical activity (yes or no) as recommended by the World Health Organization (WHO) [28].

Education attainment was measured using an adequacy score ranging from 0 to 1, which accounted for the expected years of education considering the individual's age. The score was calculated by comparing the self-declared education level to the expected level of education for the individual's age, considering the entry age in the Brazilian educational system. Scores closer to 1 represent individuals with higher educational attainment per age, and scores closer to 0 represent individuals with lower educational attainment per age.

Diet quality was evaluated by assessing 12 dietary components that comprise the BHEI-R, based on information from two 24-h dietary recalls, according to current nutritional recommendations. The dietary components include total and whole fruit, total vegetables, dark green and orange vegetables and legumes, whole grains, total grains, milk, and dairy products, meats, eggs and legumes, oils, saturated fat, sodium, and a component related to the consumption of total calories from solid fat, alcohol and added sugar (SoFAAS). Details on the assessment of components are described elsewhere [29]. Physical activity was assessed through the International Physical Activity Questionnaire (IPAQ) [30].

The adjustment baseline covariates sex, age, age^2, age−sex interaction, categorical BMI, and hypolipidemic medication use were included in the analyses performed to avoid confounding [19,31,32]. We also had the first five principal components of ancestry for population stratification, considering that the sample was obtained in a highly admixed population [33,34].

2.4. CETP SNPs

To evaluate the influence of genetic variation on HDL-c along with other cardiometabolic risk factors, this study collected information on Single Nucleotide Polymorphisms (SNPs), the most common genetic variation found in the genome.

Peripheral blood samples from 901 individuals were collected, thawed, and submitted to an automated extraction protocol in the QIAsymphony SP BioRobot with the QIAsymphony DNA Midi Kit 96 (Qiagen, Hilden, Germany) to obtain genomic DNA with EDTA stored at −80 °C at the Human Genome and Stem Cell Research Center of the University of São Paulo (IB-USP), following the manufacturer's instructions. Automated extraction was unfeasible for 40 samples with less than 1 mL of blood; therefore, a salting-out extraction protocol was used [35]. One sample with less than the required volume for the genotyping protocol was excluded from the analysis.

Quantification and quality of DNA samples were evaluated with the NanoDrop™ 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, USA) according to the criteria optical density (OD) OD 260/OD 280 between 1.8 and 2.0 and OD 260/OD 230 > 1.5. Approximately 130 samples did not present sufficient purity ratios, so they underwent a further purification process (Autopure LS - Qiagen, Hilden, Germany). Once all samples evaluated by spectrometry reached purity quality standards, their quantification was performed using the Qubit™ dsDNA BR DNA quantification Kit in the Qubit® 2.0 fluorometer (Thermo Fisher Scientific, Waltham, USA). Additionally, DNA integrity assessment through electrophoresis was performed on randomly selected samples from each batch.

Using the Axiom™ 2.0 Precision Medicine Research Array in the Thermo Fisher Scientific laboratory, genotype calling of 846 samples was made for 555,064 SNPs, among which we queried information of 15 SNPs in the CETP gene (rs5883, rs1864163, rs118146573, rs9939224, rs12691052, rs12708980, rs1532624, rs1864163, rs7499892, rs2033254, rs2303790, rs289719, rs291044, rs12708980, and rs80180245) in a candidate gene-approach fashion (Affymetrix Inc, Santa Clara, CA).

The initial sample assessment of the processing quality was performed using the Axiom™ Analysis Suite software, and five individuals were excluded due to a call rate <0.95. After sample and SNP quality control using PLINK 2.0 and Affymetrix Power Tools (APT 1.16.0) according to the Affymetrix best practices QC criteria [36], 841 individuals had genetic information on the aforementioned CETP SNPs.

Furthermore, considering that the source of the sample is a highly admixed population, we controlled for population stratification using a larger panel of SNPs across the whole genome for estimation of principal components of ancestry utilizing the *software* PLINK 2.0 0 and R (package SNPRelate) [37].

2.5. Descriptive and inferential analysis

None of the variables had normal distribution according to the Shapiro−Wilk test, therefore, continuous variables were presented in median and interquartile range. Categorical variables were presented in frequency and 95% confidence interval for proportions.

Differences in lipid traits between age groups were assessed through the non-parametric test Kruskal Wallis and post-hoc Wilcoxon test due to the absence of a normal distribution, and FDR multiple test correction was adopted.

Pairwise correlation analysis was performed using the Spearman method, considering absolute values of the correlation coefficients within the ranges 0−39, 40−69, and 70−100 as low, moderate, and high correlations, respectively.

The underlying structure of the lipid profile was evaluated through Principal Component Analysis (PCA) across age groups and according to the presence or absence of any dyslipidemia. This and all further analyses were performed using R software v4.0.2 and Python 3.6, adopting a significance level of 0.05.

2.6. Statistical modeling

After excluding closely related individuals who shared the same household, we obtained a subsample of 707 independent observations. After excluding missing data, the dataset had a total of 631 individuals. Univariate analysis with multiple linear and logistic regression was performed for quantitative lipid phenotypes and DLP adjusted by hypolipidemic medication use, respectively. The non-genetic variables selected by a pre-screening science driven-approach were sorted into six classes: inflammatory; insulin, and glucose-related variables; anthropometric; lifestyle; socioeconomic and demographic characteristics; and cardiac-related risk factors.

Since residual analysis showed not normally distributed residuals, lipid traits were transformed with the Rank-Based Normal Inverse Transformation, which has been extensively and suitably used for modeling approaches that may include genetic variants [38–40].

Models were adjusted using a stepwise approach for initial selection for each lipid trait and within the six classes of dependent variables, including base adjustment covariates to avoid confounding. The top five principal components of ancestry were also used as base covariates in all model adjustments, as in Fu et al. (2021) [34]. Statistically significant variables were then combined in a final model fit.

Then, we investigated a panel of 15 SNPs in the CETP gene, which plays a major role in the balance between HDL and Apo-B-rich lipoprotein (VLDL, IDL, and LDL) metabolism. Considering each SNP as a 3-level factor (three possible genotypes; two degrees of freedom), we checked whether these markers would be associated with HDL-c concentrations and low HDL-c levels in the ISA dataset and if the inclusion of this genetic information would increase the accuracy of the final non-genetic model, tests performed under $\alpha = 0.05$.

3. Results

3.1. Prevalence and correlation analysis

Most individuals self-reported white or brown skin color (50.28 % and 32.84 %, respectively). There was a higher prevalence of individuals attaining recommended global physical activity among adults and older adults compared to adolescents. Overweight prevalence (45.04 %) was different across age groups, being higher in adults and older adults than adolescents (Table 1).

Low HDL-c and DLP adjusted by lipid-lowering drugs use were the most prevalent dyslipidemias in the population of São Paulo (58.98 % and 65.76 %, respectively), presenting high prevalence in different age groups. There was a significantly higher prevalence of DLP adjusted by lipid-lowering drug use among adults and older adults in comparison to adolescents (Table 1).

Descriptive statistics of quantitative demographic, diet quality index, and cardiovascular risk factors for the total sample and according to age groups are presented in Tables 2 and 3. The comparison between age groups showed that, except for plasma HDL-c concentration, there was a significant difference in biomarkers between adolescents and the other age groups. Still, there was no statistical difference between adults and older adults (Table 3).

Low linear relationships were identified between most variables, according to the heatmaps of pairwise correlations, showing mostly low and some moderate correlations (Fig. 1 and Supporting Material 1).

3.2. Principal component analysis

Principal Component Analysis (PCA) of lipid traits stratified by age group showed that adolescents, adults, and older adults presented similar lipid profiles (Fig. 2A). The first and the second principal components explained 57.30 % and 23.50 % of the variance, respectively, whilst the third principal component accounted for 17.87 %. The relationship between principal components 1 and 2 is presented in Fig. 2.

Variables with the highest loadings (contributions) in the first principal component were non-HDL-c, total cholesterol and LDL-c, whilst HDL-c, TGL, and VLDL-c presented the highest loadings in the second principal component, and HDL-c and LDL-c/HDL-c ratio were the highest contributors to the third principal component. Once stratified by the presence or absence of any dyslipidemia, this analysis showed two distinct groups with some overlapping (Fig. 2B).

3.3. Model fits

3.3.1. Linear regression

Overall, the adjusted R^2 range was 0.121–0.271 in the models (Supporting Material 3), presenting a lower performance for HDL-c compared to other lipid traits. The covariates included in each final model and their respective coefficients are shown in Table 4 (p-value <0.05).

Regarding clusters of explanatory variables, except for age, neither the demographic nor socioeconomic covariates presented statistical significance. Among lifestyle characteristics, two dietary components were significant in the final models (e.g., SoFAAS and sodium for HDL-c fit), in addition to tobacco use and recommended physical activity during leisure.

The presence of overweight showed significant positive associations with outcome variables, whereas other anthropometric measures showed no association. Concerning inflammatory biomarkers, CRP, MCP-1, and TNF-α presented statistical significance. In relation to glucose-related variables, insulin resistance, and glucose were significant for several lipid traits, whilst insulin levels were only significant for HDL-c. SBP was significantly associated with HDL-c, LDL-c/HDL-c, and TGL, while DBP was related to LDL-c, VLDL-c, and total cholesterol.

3.3.2. Logistic regression

The area under the ROC curve (AUC) and odds ratio (OR) for any dyslipidemia are displayed in Table 5. There was minimal variation in the AUC among classes of explanatory variables (0.71–0.72) (Data not shown) and a slight increase in the accuracy of the final selected model (0.74). Remarkably, only a few tested covariates were significant in the final model. Categorical BMI and insulin resistance were positively associated with any dyslipidemia, with 1.99 and 1.75 ORs, respectively, while SBP was slightly associated.

3.3.3. HDL-c and CETP SNPs association

Table 6 shows the minor alleles and genotype frequencies for the SNPs evaluated. Among the 15 SNPs tested, 4 were significantly associated with HDL-c levels. Compared to the homozygosity of the minor allele and having fixed all the other covariates included in the model, for rs7499892, homozygosity of the T allele was inversely associated with HDL-c, as opposed to rs12691052, rs291044, and rs80180245, whose heterozygosity was inversely associated with the evaluated phenotype (Table 7). Additional analysis showed a significant interaction effect between rs291044

Table 1
Socioeconomic, demographic, and lifestyle characteristics of individuals in the city of Sao Paulo, Brazil. ISA-Capital, 2015.

Characteristic	Total			Adolescent			Adult			Older Adult		
	N	%	95%CI	N	%	95%CI	N	%	95%CI	N	%	95%CI
Age (years)§	901	43.00	17–63	291	15	13–17	303	42	34–51	307	68	63–74.5
Sex	901			291			303			307		
Male	446	49.5	46.25–52.76	141	48.45	42.78–54.17	154	50.82	45.22–56.40	151	49.19	43.64–54.75
Female	455	50.5	47.24–53.75	150	51.54	45.82–57.23	149	49.17	43.59–54.78	156	50.81	45.25–56.36
Ethnicity	889			287			302			300		
White	447	50.28	47.00–53.56	120	41.81	36.25–47.59	155	51.32	45.71–56.91	172	57.33	51.68–62.80
Black	95	10.68	8.82–12.89	36	12.54	9.20–16.87	31	10.26	7.33–14.20	28	9.33	6.53–13.16
Yellow	13	1.46	0.85–2.49	2	0.7	0.19–2.50	3	1	0.33–2.88	8	2.66	1.36–5.17
Brown	292	32.84	29.83–36.0	116	40.41	34.90–46.19	101	33.44	28.36–38.94	75	25	20.44–30.20
Indigenous	2	0.22	0.04–0.81	0	0	0	1	0.33	0.06–1.86	1	0.33	0.06–1.86
Other	40	4.49	3.32–6.07	13	4.53	2.67–7.59	11	3.64	2.05–6.41	16	5.33	3.31–8.49
Education score§	895	0.75	0.375–1	290	1	1–1	302	0.75	0.44–0.8	303	0.31	0.25–0.75
BMI	888			286			300			302		
<25 kg/m^2	488	54.95	51.67–58.2	200	69	64.38–74.95	121	40.34	34.03–45.97	167	55.3	49.66–60.80
≥25 kg/m^2	400	45.05	41.8–48.3	86	31	25.05–35.62	179	59.66	54.03–65.06	135	44.7	39.19–50.34
Smoking	895			290			302			303		
Never smoked	638	71.28	68.23–74.15	276	95.17	89.79–95.58	181	59.93	54.32–65.30	181	59.74	54.13–65.10
Former smoker	147	16.43	14.14–19.00	5	1.72	0.72–3.89	57	18.87	14.86–23.67	85	28.05	23.29–33.36
Current smoker	110	12.29	10.30–14.60	9	3.1	1.61–5.68	64	21.19	16.96–26.15	37	12.21	8.99–16.38
Alcohol use	893	23.07	20.42–25.94	289	8.3	5.64–12.06	301	34.22	29.09–39.75	303	26.07	21.45–31.29
Leisure PA	896	18.75	16.32–21.44	290	18.28	14.25–23.13	302	21.19	16.96–26.15	304	16.77	13.00–21.39
Leisure PA (min/week)§	888	0.00	0–135	287	90	0–245	300	0	0–108.8	301	0	0–60
Global PA	881	68.56	65.42–71.54	286	50.7	44.93–56.44	296	82.77	78.05–86.64	299	71.57	66.21–76.39
Global PA (min/week)§	881	450.00	160–1080	286	382.5	170–870	296	660	227.5–6720	299	400.00	110–887.5
Household income per capita§	901	342.00	114.5–666.3	291	234.3	72.88–432.81	303	374.8	165.3–749.6	307	460.7	116–851.1

Obs.: (§) Median and interquartile range; DLP = any dyslipidemia; BMI = Body Mass Index; Leisure PA = recommended level of physical activity during leisure; Global PA = recommended level of global physical activity.

Table 2
Diet, anthropometric, and cardiovascular-related characteristics of individuals in the city of São Paulo, Brazil. ISA-Capital, 2015.

Characteristic	Total			Adolescent			Adult			Older adult		
	N	Median	IQR	N	Median	IQR	N	Median	IQR	N	Median	IQR
Diet quality												
BHEI-R	891	66.09	60.97–70.65	288	63.06	57.66–67.14	298	65.61	61.05–69.96	305	69.49	65.12–73.04
Cereals	891	0.28	0.20–0.73	288	0.26	0.20–0.37	298	0.28	0.20–0.91	305	0.29	0.20–1.12
Fat	891	8.07	6.54–8.65	288	8.06	6.48–8.56	298	8.08	6.41–8.62	305	8.09	6.63–8.73
Grains	891	5.00	5.0–5.0	288	5.00	5.0–5.0	298	5.00	5.0–5.0	305	5.00	5.0–5.0
Green and orange	891	5.00	5.0–5.0	288	5.00	5.0–5.0	298	5.00	5.0–5.0	305	5.00	5.0–5.0
Meat	891	10.00	9.95–10.0	288	10.00	10.0–10.0	298	10.00	9.95–10.0	305	10.00	9.93–10.0
Milk and dairy	891	5.04	3.44–6.63	288	4.67	3.14–6.10	298	4.81	3.25–6.70	305	5.59	4.27–7.20
Oil	891	10.00	10.0–10.0	288	10.00	10.0–10.0	298	10.00	10.0–10.0	305	10.00	10.0–10.0
Sodium	891	2.12	0.83–3.44	288	2.55	1.24–3.67	298	2.05	0.58–3.58	305	2.08	0.74–3.16
SoFAAS	891	9.58	6.34–12.43	288	7.70	4.82–10.73	298	9.57	6.07–12.53	305	11.1	8.11-13-69
Total fruit	891	4.96	2.57–5.0	288	3.53	2.11–5.0	298	4.34	2.20–5.0	305	5	4.38–5
Total vegetables	891	5.00	5.0–5.0	288	5.00	5.0–5.0	298	5.00	5.0–5.0	305	5.00	5.0–5.0
Whole fruit	891	3.76	1.97–5.0	288	2.72	1.55–4.5	298	3.7	1.87–5	305	4.99	3.11–5
Waist circumference (cm)	885	90.00	76.50–101	287	74	68.25–83.85	296	92.17	82.42–101.09	302	98.67	91–106.57
Waist/height	879	0.55	0.46–0.62	285	0.45	0.42–0.51	294	0.55	0.49–0.61	300	0.61	0.55–0.67
Glucose (mg/dL)	898	94.00	88–104	290	89	85–94.75	302	95	88–103	306	103	93–117
HOMA-IR	892	2.60	1.74–4.07	289	2.61	1.82–3.93	300	2.49	1.57–4.00	303	2.77	1.79–4.32
Insulin (IU/mL)	894	11.00	7.50–16.44	290	11.7	8.30–17.07	301	10.4	6.9–16.6	303	10.1	7.05–15.45
SBP (mmHg)	891	124.33	113.75–139.58	286	113.5	106.37–122	302	124	115.67–135	303	141	128.33–156
DBP (mmHg)	891	75.50	67.58–83	286	68	62.62–75.92	302	78	70–85.667	303	79.5	72–85.667
MCP1 (pg/mL)	872	276.00	251.00–314	282	243	189.25–312	296	279.5	216.75–343	294	311.5	245.25–389.25
CRP (mg/L)	872	0.27	0.09–0.73	282	0.09	0.06–0.30	296	0.32	0.15–0.81	294	0.44	0.20–0.98
TNF-α (pg/mL)	872	11.09	8.20–14.28	282	11.05	8.18–14.09	296	9.98	7.54–12.69	294	12.26	9.11–16.49
IL-6 (pg/mL)	872	1.37	0.97–2.96	282	1.45	1–5.322	296	1.17	0.89–2.38	294	1.48	1.04–2.50
IL-1β (pg/mL)	872	1.17	0.91–1.52	282	1.27	0.96–1.61	296	1.1	0.9–1.5	294	1.15	0.88–1.47
IL-10 (pg/mL)	872	4.26	3.03–6.76	282	4.96	3.44–7.95	296	3.8	2.54–5.5	294	4.26	3.06–6.87
DLP†	881	62.54	59.30–66.00	288	55.21	49.43–60.84	298	67.11	61.60–72.20	295	65.08	59.48–70.29
DLP (drug adjusted)†	885	65.76	62.30–68.81	288	55.21	49.43–60.84	289	69.46	64.01–74.41	299	72.24	66.91–77.01
Isolated hypercholesterolemia†	880	2.05	1.30–3.21	288	0.69	0.19–2.50	297	2.36	1.15–4.78	295	2.03	0.93–4.36
Isolated hypertriglyceridemia†	881	1.7	1.03–2.79	288	0.69	0.19–2.50	298	1.68	0.71–3.86	295	2.71	1.38–5.26
Mixed hyperlipidemia†	880	1.02	0.54–1.93	288	0	0	297	2.36	1.15–4.78	295	0.68	0.12–2.44
Low HDL†	880	58.98	55.70–62.18	288	52.78	47.01–58.47	297	62.62	57–67.93	295	61.35	55.69–66.73

Obs.: (†) Proportion and 95% confidence interval; HOMA-IR = Insulin resistance index; MCP1 = Monocyte chemoattractant protein; CRP = C-reactive protein; TNF-α = Tumor necrosis factor α; ILβ (pg/mL) = Interleukin 1β; IL-6 (pg/mL) = Interleukin 6; IL10 (pg/mL) = Interleukin 10; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; Global PA = Global physical activity; Leisure PA = Leisure physical activity; SoFAAS = Calories coming from solid fat, added sugar and alcohol; IQR = Interquartile range.

Table 3
Differences in lipid traits between age groups in the city of São Paulo, Brazil. ISA-Capital 2015.

Characteristic	Total			Adolescent			Adult			Older Adult		
	Median	IQR	Sig.	Median	IQR	Sig.*	Median	IQR	Sig.§	Median	IQR	Sig.†
Triglycerides (mg/dL)	99.00	71–138	0.000	76.00	58–102	0.000	107.00	77.25–153.75	0.054	114.00	87.5–157	0.000
Total cholesterol (mg/dL)	166.00	139–197	0.000	140.00	123–161.2	0.000	181.00	153–206	0.318	184.00	156.5–210.5	0.000
HDL-c (mg/dL)	43.00	35–53	0.412	44.00	37–51	0.402	42.00	33–53	0.402	43.00	35.5–52.5	0.932
LDL-c/HDL-c	2.32	1.61–3.12	0.000	1.81	1.43–2.42	0.000	2.67	1.86–3.61	0.250	2.57	1.83–3.31	0.000
LDLc (mg/dL)	98.00	76–125	0.000	79.00	65.75–95	0.000	110.00	88–134	0.901	111.00	86–135	0.000
Non-HDL-c (mg/dL)	120.00	94–152	0.000	96.00	80–114	0.000	137.00	107–161	0.749	136.00	110–165.5	0.000
VLDLc (mg/dL)	20.00	14–28	0.000	15.00	12–20	0.000	21.00	15–31	0.043	23.00	17.5–31.5	0.000

Obs.: (*) Difference between adolescents and adults; (†) Difference between adolescents and older adults; (§) Difference between adults and older adults. 0 values represent extremely low *p*-values; IQR = Interquartile range.

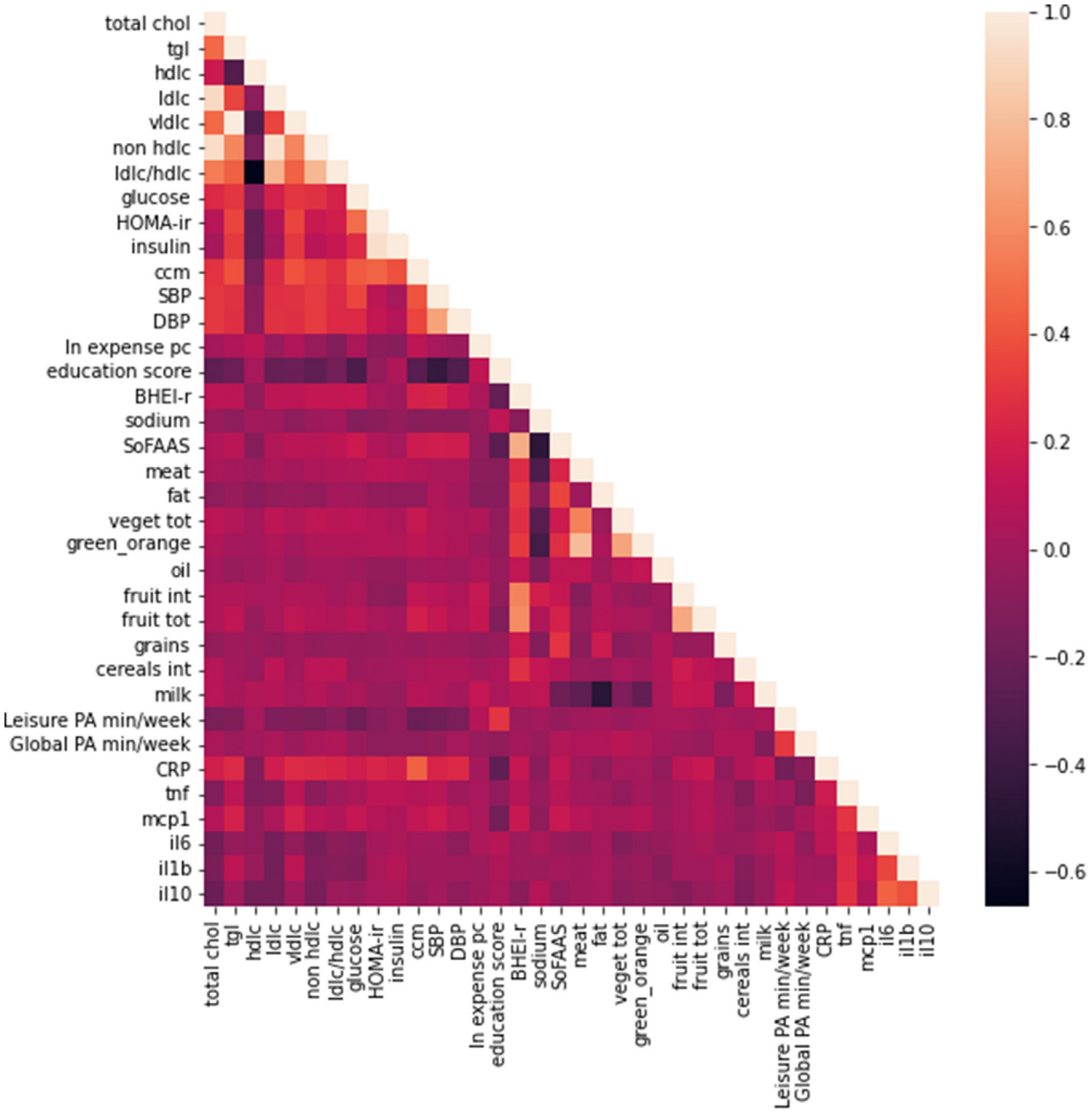

Fig. 1. Correlation heatmap of lipid traits and other cardiometabolic risk factors.
Obs.: HOMA-ir = Insulin Resistance Index; CRP = C-reactive protein; tnf = Tumor necrosis factor α; il1b = interleukine 1β; il6 = interleukine 6; il10 = interleukine 10; mcp1 (monocyte chemoattractant protein 1); ccm = Waist Circumference; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BHEI-r = Brazilian Healthy Eating Index Revised; SoFAAS = Calories coming from solid fat, added sugar and alcohol; Leisure PA min/week = Time spent in leisure physical activity per week, Leisure PA min/week = Time spent in global physical activity per week.

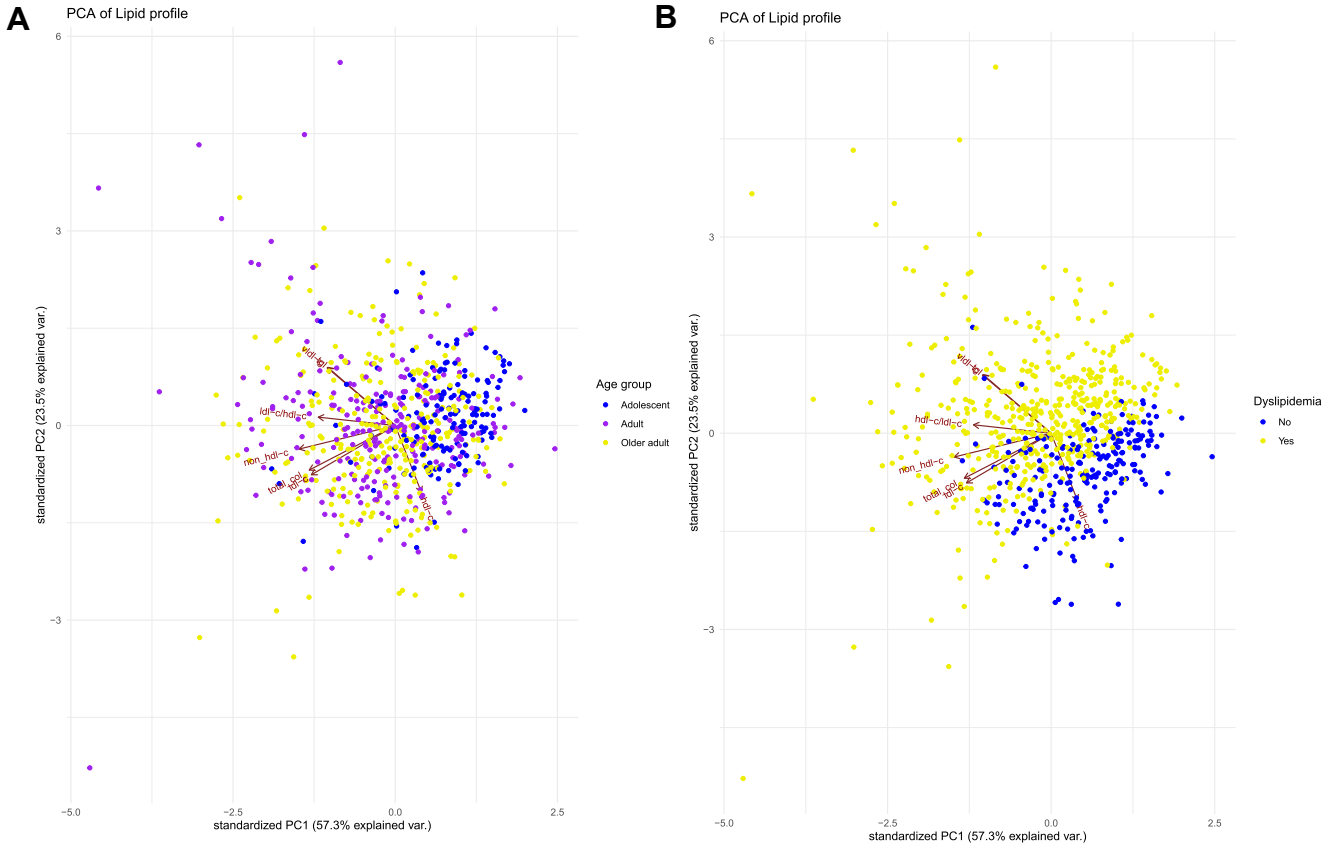

Fig. 2. Principal Components Analysis of lipid profile according to age group (A) and presence or absence of dyslipidemia (B) in individuals living in São Paulo, Brazil.
Obs.: Lipid profile based on total cholesterol, VLDL-c, LDL-c, HDL-c, non-HDL-c, LDL-c/HDL-c and triglycerides. PC1 = first principal component; PC2 = second principal component.

and the dietary component SoFAAS on HDL-c levels under $\alpha = 0.05$ (Results not shown).

The adjusted R^2 in the HDL-c model rose from 0.12 to 0.18 after the inclusion of these markers, which represents a 50 % increase in the variance explanation accounted by non-genetic variables.

Furthermore, after initial covariate selection through the stepwise approach for low HDL-c levels (selected covariates were categorical BMI, insulin resistance, and PC3), there were also significant associations between low HDL-c levels and 4 CETP SNPs (rs7499892, rs291044, rs2033254, and rs289719) with odds ratios ranging from 0.07 to 4.13 (Table 8).

4. Discussion

The study's results showed similarities in the occurrence of dyslipidemia among adults and elderly individuals and similar lipid profiles among all age groups in São Paulo, Brazil. It is particularly worrying that adolescents showed low HDL-c concentrations and tended to present lipid profiles similar to older individuals, potentially indicating unhealthy lifestyle choices that will influence health into adulthood.

The high prevalence of dyslipidemia phenotypes in our investigation reinforces the results from previous studies with African and Mexican populations [32,41]. However, evidence on the prevalence of dyslipidemia among Middle-Eastern and Asian adolescents showed a predominance of low HDL-c and hypertriglyceridemia as opposed to our results, which only showed a high prevalence for low HDL-c [42,43]. Nonetheless, it is important to highlight differences in the criteria for defining dyslipidemia and the design adopted across studies, which probably account for the different results.

More importantly, it should be noted that the prevalence of dyslipidemias in the population of São Paulo has increased over the years and is approximately twice the one reported in US teenagers [20,44]. Furthermore, the absence of differences in HDL-c concentrations between age groups in this study indicated similar risk profiles, previously shown in another Brazilian cohort [45].

Concerning other lipid traits, there were significant differences between adolescents with regard to adults and older adults, potentially linked to differences in hormone regulation (e.g., testosterone, dehydroepiandrosterone, and somatotropin) and lipid metabolism in diverse life stages [46]. In addition, adolescents present reduced exposure time to lifestyle risk factors (e.g., smoking, alcohol use, exposure to pollutants, among others) in comparison to adults and older adults. However, other studies showed that Brazilian adolescents usually present unhealthy lifestyles marked by low physical activity, low diet quality, and high sedentarism, independently of socioeconomic level [44].

Nonetheless, the PCA results indicated that the lipid profiles of individuals of the three age groups present high similarity. Considering the well-established association between lipid profiles and cardiovascular risk, especially in atherosclerosis, the variability in lipid traits corresponds to variability in cardiovascular risk. Thus, our results potentially indicate a higher risk for CVD in the long run for adolescents in São Paulo, considering the similarity with older individuals regarding biomarkers.

In addition, the contribution of LDL-c to the variance and the identification of triglycerides and HDL-c as relevant traits in the present study were in line with the most recent highlights on the pathophysiology of atherosclerosis [12,47–49]. For instance, the CETP-mediated exchange of cholesteryl esters and triglycerides

Table 4
Models for lipid traits according to classes of dependent variables. ISA-Capital 2015.

Trait	Independent Variables		
	Covariates	β	Sig.
LDL-c	Age	0.0561	***
	Age^2	−0.0005	***
	Hypolipemic drug use	−0.7710	***
	DBP	0.0104	**
HDL-c	Age^2	0.0001	***
	BMI	−0.2836	***
	TNF-α	−0.0174	**
	Insulin	−0.0109	**
	Smoking (current)	−0.2854	*
	SBP	−0.0048	*
	SoFAAS	−0.0356	***
	Sodium	−0.0532	*
TGL	Age	0.0441	***
	Age^2	−0.0004	***
	Sex	0.1784	*
	BMI	0.2258	**
	PC3	−63.9500	***
	PC4	−25.7500	**
	Insulin resistance	0.4304	***
	MCP1	0.0007	**
	SBP	0.0048	*
	Leisure PA	−0.0002	**
VLDL-c	Age	0.0366	***
	Age^2	−0.0003	***
	Sex	0.1778	*
	BMI	0.2384	**
	Insulin resistance	0.4315	***
	PC3	−62.7600	***
	PC4	−25.0500	***
	Smoking (current)	0.2140	*
	MCP1	0.0007	**
	SBP	0.0078	*
	Leisure PA	−0.0002	*
Non-HDL-c	Age	0.0700	***
	Age^2	−0.0006	***
	BMI	0.2100	**
	Hypolipemic drug use	−0.6379	***
	PC1	−8.4400	*
	Glucose	0.0025	**
Total cholesterol	Age	0.0643	***
	Age^2	−0.0005	***
	Hypolipemic drug use	−0.5713	***
	Glucose	0.0020	*
	DBP	0.0116	***
LDL-c/HDL-c	Age	0.0436	***
	Age^2	−0.0004	***
	BMI	0.3003	**
	Hypolipemic drug use	−0.6782	***
	PC1	−8.7210	*
	Glucose	0.0019	*
	CRP	0.1602	*
	SBP	0.0072	***

between triglyceride-rich lipoproteins (TRLs) and other lipoproteins, such as HDL, might lead to increased cardiometabolic risk through several mechanisms, which include inflammatory cascades, structural alterations in LDL, resulting in smaller, dense LDL fractions, and interactions with matrix proteoglycans of the endothelial cells through apolipoproteins such as ApoB. Particularly, apoB48-remnant lipoproteins have already been associated with increased cardiometabolic risk in adolescents [49,50].

Table 5
Logistic regression model for dyslipidemia. ISA-Capital 2015.

Trait	Covariate	OR	Sig.
DLP (drug adjusted)	BMI	1.99	***
	PC3	3.96E-21	*
	Insulin resistance	1.75	**
	SBP	1.02	**
AUC	0.74		

Obs.: * < 0.05; ** < 0.01; *** < 0.001; DLP = Any dyslipidemia; AUC = Area under the ROC curve; PC = Principal component; BMI = Body Mass Index.

Similar to the contribution of HDL-c found in our PCA results, the extremely low percentages of variance explanation for HDL-c in our models strongly suggest that additional factors might not have been accounted for yet, e.g., genetic characteristics. For instance, moderate to high heritabilities have been reported for HDL-c worldwide and in Brazil (31.2 %), meaning that there is a significant genetic component underlying this trait, which might account for part of the unexplained variance in our models [51–53].

This hypothesis is supported by the fact that, while the variance explained for LDL-c is higher than HDL-c one, the heritability estimates found for LDL-c are lower than for HDL-c [52,54,55]. In our study, we showed a considerable genetic contribution to HDL-c concentrations, as evidenced by a significant increase in the explained variance of this trait after the inclusion of four SNPs. Significantly, rs7499892 and rs291044 were also associated with the binary phenotype low HDL-c level, which further strengthens their potential contribution. Since these markers are primarily present in intronic regions of the CETP gene, we cannot infer whether they alter CETP function or are spurious associations due to linkage disequilibrium with true causal variants in neighbor regions of the gene. Nonetheless, their reducing effects on HDL-c levels suggest that this gene may play an even more pivotal role in HDL-c metabolism and cardiovascular risk in the context of the Brazilian population.

Other CETP SNPs have been shown to influence HDL-c, mainly through dietary interactions. For instance, the intake of trans fatty acids increases CETP activity, which might reduce HDL-c concentrations [16,56–58]. Herein, we found that calories within the SoFAAS dietary component, which includes fat rich in SFA and trans fatty acids, were also associated with HDL-c concentrations. Additional modeling analysis identified a significant interaction effect between this dietary component and rs291044 in the ISA dataset under $\alpha = 0.05$. This suggests a possible synergistic effect between diet and genetic variation on the CETP gene.

Furthermore, it is important to highlight that the majority of studies have been conducted in Caucasian populations [16], which implies that: (1) our study provides novel insights into the genetics of CETP in a population with mixed ethnicity; (2) comparisons must be made with caution because of difference in study design and population; (3) further replication and elucidation are necessary using testing larger datasets from future follow-ups of the ISA Nutrition Survey and other studies.

Our results show that being overweight, insulin resistance, and lifestyle characteristics, including consuming solid fat, added sugar, alcohol, and sodium, physical activity, and smoking, comprise suitable predictors of lipid traits, especially HDL-c, and dyslipidemia. Remarkably, except for CRP, MCP-1, and TNF-alpha in the linear regression models, inflammatory biomarkers were not significantly associated with lipid traits. This weak influence was confirmed by the lack of visually distinct clusters in the PCA performed with these biomarkers (Supporting Material 2). These later findings contrast with several studies that consistently showed a strong relationship between lipid traits and inflammation in the development of cardiovascular disorders [12,59,60]. A possible explanation for those contrasting results refers to the criteria for defining dyslipidemias in the Brazilian population, which might not entirely reflect the underlying inflammatory mechanisms that potentially influence the individuals' cardiovascular risk.

The limitations of the present study include mainly issues related to the survey design and data availability. One limitation refers to the unavailability of data on other CETP markers, which

Table 6
Single nucleotide polymorphisms (SNPs) in the CETP gene available from ISA-Capital 2015 genotype SNP data.

SNP	Minor Allele	Heterozygous	Homozygous Dominant	Homozygous Recessive
rs12691052	A	6.9 %	0.4 %	92.7 %
rs7499892	T	34.4 %	5.9 %	59.7 %
rs291044	A	44.4 %	11.2 %	44.4 %
rs80180245	T	3.0 %	0.0 %	97.0 %
rs1864163	A	42.4 %	7.9 %	49.7 %
rs118146573	A	18.0 %	0.8 %	81.2 %
rs9939224	T	35.4 %	6.9 %	57.7 %
rs12708980	G	43.3 %	11.1 %	45.6 %
rs1532624	A	45.8 %	6.2 %	48.0 %
rs5883	T	10.7 %	0.2 %	89.1 %
rs289719	T	42.6 %	8.9 %	48.5 %
rs2033254	C	42.5 %	9.9 %	47.6 %
rs5880	C	7.7 %	0.0 %	92.3 %
rs5742907	A	0.2 %	0.0 %	99.8 %
rs2303790	G	0.5 %	0.0 %	99.5 %

Table 7
Single nucleotide polymorphisms (SNPs) in the CETP gene associated with HDL-c levels. ISA-Capital 2015.

SNP	Minor Allele	β	Sig.
rs12691052	A	−0.54	0.0004
rs7499892	T	−0.74	0.0000
rs291044	A	−0.24	0.0040
rs80180245	T	−0.74	0.0012

Table 8
Single nucleotide polymorphisms (SNPs) in the CETP gene associated with low HDL-c levels. ISA-Capital 2015.

SNP/Genotype	Minor Allele	OR	Sig.
rs7499892 - Homozygous	T	4.13	0.0060
rs2033254 - Heterozygous	C	0.29	0.0020
rs2033254 - Homozygous	C	0.07	0.0008
rs289719 - Heterozygous	T	0.25	0.0004
rs289719 - Homozygous	T	0.08	0.0005
rs291044 - Heterozygous	A	0.47	0.0402
rs291044 - Homozygous	A	0.12	0.0034

Obs.: Model adjusted for categorical BMI, The 3rd. principal component of ancestry and insulin resistance.

could potentially lead to insights on the relationships among genes, dyslipidemia, and CVD phenotypes. In addition, due to its cross-sectional observational nature, it is not possible to establish causality in the analyses conducted. Therefore, the interpretation of the results must be cautious. Concerning data availability, specific characteristics of individuals in the sample were absent in data collection; thus, analyses involving other lipid traits could not be performed, such as the measurement of apolipoproteins commonly associated with CVD risk, including apoB48, apoB100, apoC-III, and LDL fractions [49,61].

The study's results include evidence that may be used to support the design of public policies toward the change in modifiable risk factors of individuals in the Brazilian population, especially adolescents. The influence of lifestyle characteristics such as diet and physical activity, as well as insulin resistance and BMI on cardiometabolic risk, represents worrisome evidence on expected long-term health outcomes of the population of São Paulo, indicating the need for public health interventions at the primary care level to redirect lifestyle choices towards healthy behaviors, reducing the burden of CVD in Brazil.

5. Conclusion

Similar lipid profiles were observed among adolescents, adults, and older adults living in São Paulo in 2015. These profiles suggest potential trends towards an increased risk of developing cardiovascular diseases and other related conditions in later stages of life for adolescents, as compared to adults and older adults. This risk can primarily be attributed to reduced HDL-c concentrations, which seem to be influenced by genetic components in the CETP gene and possibly gene–diet interactions. The findings contribute to the investigation of dyslipidemia and its association with other CVD risk factors in a highly admixed Brazilian population, which may guide public health policies towards the promotion of healthy lifestyles and prevention of diseases at the primary care level, averting risks for early mortality and loss of quality of life in the country.

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.10.002.

References

[1] Malta DC, Moura L de, Prado RR, Escalante JC, Schmidt MI, Duncan BB. Chronic non-communicable disease mortality in Brazil and its regions, 2000-2011. Epidemiol e Serviços Saúde 2014;23:599–608. https://doi.org/10.5123/S1679-49742014000400002.

[2] World Health Organization (WHO). Global status report on noncommunicable diseases 2014. 2014. Geneva.

[3] Lin H-Q, Wu J-Y, Chen M-L, Chen F-Q, Liao Y-J, Wu Y-T, et al. Prevalence of dyslipidemia and prediction of 10-year CVD risk among older adults living in southeast coastal regions in China: a cross-sectional study. Clin Interv Aging 2019;14:1119–29. https://doi.org/10.2147/CIA.S207665.

[4] Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis. Curr Opin Lipidol 2016;27:473–83. https://doi.org/10.1097/MOL.0000000000000330.

[5] Beverly JK, Budoff MJ. Atherosclerosis: pathophysiology of insulin resistance, hyperglycemia, hyperlipidemia, and inflammation. J Diabetes 2020;12:102–4. https://doi.org/10.1111/1753-0407.12970.

[6] Xi Y, Niu L, Cao N, Bao H, Xu X, Zhu H, et al. Prevalence of dyslipidemia and associated risk factors among adults aged ≥35 years in northern China: a cross-sectional study. BMC Publ Health 2020;20:1068. https://doi.org/10.1186/s12889-020-09172-9.

[7] Nirwan R, Singh D. Distribution of lipids and prevalence of dyslipidemia among Indian expatriates in Qatar. J Lipids 2021;2021:1–9. https://doi.org/10.1155/2021/8866784.

[8] De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, et al. High-density lipoprotein mediates the anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol 2014;15:152–60. https://doi.org/10.1038/ni.2784.

[9] Oki E, Norde MM, Carioca AAF, Ikeda RE, Souza JMP, Castro IA, et al. Interaction of SNP in the CRP gene and plasma fatty acid profile in inflammatory pattern: a cross-sectional population-based study. Nutrition 2016;32:88–94. https://doi.org/10.1016/j.nut.2015.07.015.

[10] Maintinguer Norde M, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, et al. Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. Clin Nutr 2018;37:659–66. https://doi.org/10.1016/j.clnu.2017.02.009.

[11] Ahmad F, Leake DS. Lysosomal oxidation of LDL alters lysosomal pH, induces senescence, and increases secretion of pro-inflammatory cytokines in human macrophages. J Lipid Res 2019;60:98–110. https://doi.org/10.1194/jlr.M088245.

[12] Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at low LDL: remnants, lipoprotein(a), and inflammation. Clin Chem 2021;67:143–53. https://doi.org/10.1093/clinchem/hvaa252.

[13] Pinheiro-de-Sousa I, Fonseca-Alaniz MH, Teixeira SK, Rodrigues MV, Krieger JE. Uncovering emergent phenotypes in endothelial cells by clustering of surrogates of cardiovascular risk factors. Sci Rep 2022;12:1372. https://doi.org/10.1038/s41598-022-05404-7.

[14] Willer CJ. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274–83. https://doi.org/10.1038/ng.2797.

[15] Tam CHT, Lim CKP, Luk AOY, Ng ACW, Lee H, Jiang G, et al. Development of genome-wide polygenic risk scores for lipid traits and clinical applications for dyslipidemia, subclinical atherosclerosis, and diabetes cardiovascular complications among East Asians. Genome Med 2021;13:29. https://doi.org/10.1186/s13073-021-00831-z.

[16] Wuni R, Kuhnle GGC, Wynn-Jones AA, Vimaleswaran KS. A Nutrigenetic update on CETP gene-diet interactions on lipid-related outcomes. Curr Atherosclerosis Rep 2022;24:119–32. https://doi.org/10.1007/s11883-022-00987-y.

[17] Deng S, Liu J, Niu C. HDL and cholesterol ester transfer protein (CETP). In: Adv. Exp. Med. Biol. - HDL metab. Dis. Springer Singapore; 2022. p. 13–26. https://doi.org/10.1007/978-981-19-1592-5_2.

[18] Talayero BG, Sacks FM. The role of triglycerides in atherosclerosis. Curr Cardiol Rep 2011;13:544–52. https://doi.org/10.1007/s11886-011-0220-3.

[19] Graham SE, Clarke SL, Wu K-HH, Kanoni S, Zajac GJM, Ramdas S, et al. The power of genetic diversity in genome-wide association studies of lipids. Nature 2021. https://doi.org/10.1038/s41586-021-04064-3.

[20] Pereira JL, Mattei J, Isasi CR, Van Horn L, Carnethon MR, Daviglus ML, et al. Diet quality, excess body weight and cardiometabolic risk factors in adolescents living in São Paulo, Brazil and the USA: differences and similarities. Publ Health Nutr 2021;24:4091–101. https://doi.org/10.1017/S1368980020002736.

[21] Pereira JL, de Castro MA, Leite JMRS, Rogero MM, Sarti FM, César CLG, et al. Overview of cardiovascular disease risk factors in adults in São Paulo, Brazil: prevalence and associated factors in 2008 and 2015. Int J Cardiovasc Sci 2021. https://doi.org/10.36660/ijcs.20210076.

[22] Mello AV, de Sarti FM, Pereira JL, Goldbaum M, Cesar CLG, Alves MCGP, et al. Determinants of inequalities in the quality of Brazilian diet: trends in 12-year population-based study (2003-2015). Int J Equity Health 2018;17:72. https://doi.org/10.1186/s12939-018-0784-2.

[23] Pereira JL, Vieira DA dos S, Alves MCGP, César CLG, Goldbaum M, Fisberg RM. Excess body weight in the city of São Paulo: panorama from 2003 to 2015, associated factors and projection for the next years. BMC Publ Health 2018;18:1332. https://doi.org/10.1186/s12889-018-6225-8.

[24] Fisberg R, Sales C, Fontanelli M, Pereira J, Alves M, Escuder M, et al. 2015 health survey of São Paulo with Focus in nutrition: rationale, design, and procedures. Nutrients 2018;10:169. https://doi.org/10.3390/nu10020169.

[25] Sociedade Brasileira de Cardiologia. I Diretriz de Prevenção da Aterosclerose na Infância e na Adolescência. Arq Bras Cardiol 2005;85.

[26] Sociedade Brasileira de Cardiologia. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose - 2017. Arq Bras Cardiol 2017;109.

[27] World Health Organization (WHO). BMI-for-age (5-19 years). 2021. https://www.who.int/toolkits/growth-reference-data-for-5to19-years/indicators/bmi-for-age. [Accessed 3 September 2022].

[28] World Health Organization (WHO). Global recommendations on physical activity for health. 2010.

[29] Previdelli ÁN, Andrade SC de, Pires MM, Ferreira SRG, Fisberg RM, Marchioni DM. A revised version of the Healthy Eating Index for the Brazilian population. Rev Saude Publica 2011;45:794–8. https://doi.org/10.1590/S0034-89102011005000035.

[30] IPAQ. Guidelines for data processing and analysis of the international physical activity questionnaire. 2005. https://sites.google.com/site/theipaq/scoring-protocol.

[31] Nakatsu Y, Niida S, Tanaka K, Takenaka S, Kuwabara A. The relationship between serum vitamin E level and risk factors for arteriosclerosis in Japanese postmenopausal women. J Nutr Sci Vitaminol 2020;66:213–8. https://doi.org/10.3177/jnsv.66.213.

[32] Kavishe B, Vanobberghen F, Katende D, Kapiga S, Munderi P, Baisley K, et al. Dyslipidemias and cardiovascular risk scores in urban and rural populations in north-western Tanzania and southern Uganda. PLoS One 2019;14:e0223189. https://doi.org/10.1371/journal.pone.0223189.

[33] de Andrade M, Ray D, Pereira AC, Soler JP. Global individual ancestry using principal components for family data. Hum Hered 2015;80:1–11. https://doi.org/10.1159/000381908.

[34] Fu M, Bakulski KM, Higgins C, Ware EB. Mendelian randomization of dyslipidemia on cognitive impairment among older Americans. Front Neurol 2021;12. https://doi.org/10.3389/fneur.2021.660212.

[35] Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16. https://doi.org/10.1093/nar/16.3.1215. 1215-1215.

[36] Thermo Fisher Scientific. Axiom genotyping solution data analysis user guide. Pub. No. MAN0018363 A.0; 2020. p. 1–160.

[37] Zheng X, Levine D, Shen J, Gogarten SM, Laurie C, Weir BS. A high-performance computing toolset for relatedness and principal component analysis of SNP data. Bioinformatics 2012;28:3326–8. https://doi.org/10.1093/bioinformatics/bts606.

[38] Mccaw ZR, Lane JM, Saxena R, Redline S, Lin X. Operating characteristics of the rank-based inverse normal transformation for quantitative trait analysis in genome-wide association studies. Biometrics 2020;76:1262–72. https://doi.org/10.1111/biom.13214.

[39] Diego VP, de Chaves RN, Blangero J, de Souza MC, Santos D, Gomes TN, et al. Sex-specific genetic effects in physical activity: results from a quantitative genetic analysis. BMC Med Genet 2015;16:58. https://doi.org/10.1186/s12881-015-0207-9.

[40] Leite JMRS, Soler JMP, Horimoto ARVR, Alvim RO, Pereira AC. Heritability and sex-specific genetic effects of self-reported physical activity in a Brazilian highly admixed population. Hum Hered 2019;84:151–8. https://doi.org/10.1159/000506007.

[41] Rivas-Gomez B, Almeda-Valdés P, Tussié-Luna MT, Aguilar-Salinas CA. Dyslipidemia in Mexico, a call for action. Rev Investig Clin 2018;70. https://doi.org/10.24875/RIC.18002573.

[42] Qorbani M, Djalalinia S, Farzadfar F, Hovsepian S, Kelishadi R, Naderimagham S. Prevalence of dyslipidemia in Iranian children and adolescents: a systematic review. J Res Med Sci 2015;20:503. https://doi.org/10.4103/1735-1995.163979.

[43] He H, Pan L, Du J, Liu F, Jin Y, Ma J, et al. Prevalence of, and biochemical and anthropometric risk factors for, dyslipidemia in children and adolescents aged 7 to 18 years in China: a cross-sectional study. Am J Hum Biol 2019;31. https://doi.org/10.1002/ajhb.23286.

[44] Haddad MR, Sarti FM. Sociodemographic determinants of health behaviors among Brazilian adolescents: trends in physical activity and food consumption, 2009-2015. Appetite 2020;144:104454. https://doi.org/10.1016/j.appet.2019.104454.
[45] Giolo SR, Pereira AC, de Andrade M, Krieger JE, Soler JP. Evaluating gene by sex and age interactions on cardiovascular risk factors in Brazilian families. BMC Med Genet 2010;11:132. https://doi.org/10.1186/1471-2350-11-132.
[46] Pataky MW, Young WF, Sreekumaran Nair K, Clin M. Hormonal and metabolic changes of aging and the influence of lifestyle modifications. Mayo Clin Proc 2021;96:788–814. https://doi.org/10.1016/j.mayocp.2020.07.033.
[47] Libby P. The changing landscape of atherosclerosis. Nature 2021;592:524–33. https://doi.org/10.1038/s41586-021-03392-8.
[48] Tsao CW, Vasan RS. Cohort profile: the framingham heart study (FHS): overview of milestones in cardiovascular epidemiology. Int J Epidemiol 2015;44:1800–13. https://doi.org/10.1093/ije/dyv337.
[49] Sascău R, Clement A, Radu R, Prisacariu C, Stătescu C. Triglyceride-rich lipoproteins and their remnants as silent promoters of atherosclerotic cardiovascular disease and other metabolic disorders: a review. Nutrients 2021;13:1774. https://doi.org/10.3390/nu13061774.
[50] Krysa JA, Vine DF, Beilin LJ, Burrows S, Huang R-C, Mori TA, et al. ApoB48-remnant lipoproteins are associated with increased cardiometabolic risk in adolescents. Atherosclerosis 2020;302:20–6. https://doi.org/10.1016/j.atherosclerosis.2020.04.021.
[51] de Oliveira CM, Pereira AC, de Andrade M, Soler JM, Krieger JE. Heritability of cardiovascular risk factors in a Brazilian population: baependi Heart Study. BMC Med Genet 2008;9:32. https://doi.org/10.1186/1471-2350-9-32.
[52] Giolo SR, Pereira AC, de Andrade M, Krieger JE, Soler JP. Evaluating gene by sex and age interactions on cardiovascular risk factors in Brazilian families. BMC Med Genet 2010;11:132. https://doi.org/10.1186/1471-2350-11-132.
[53] Arya R, Farook VS, Fowler SP, Puppala S, Chittoor G, Resendez RG, et al. Genetic and environmental (physical fitness and sedentary activity) interaction effects on cardiometabolic risk factors in Mexican American children and adolescents. Genet Epidemiol 2018. https://doi.org/10.1002/gepi.22114.
[54] Cadby G, Melton PE, McCarthy NS, Giles C, Mellett NA, Huynh K, et al. Heritability of 596 lipid species and genetic correlation with cardiovascular traits in the Busselton Family Heart Study. J Lipid Res 2020;61:537–45. https://doi.org/10.1194/jlr.RA119000594.
[55] Akbarzadeh M, Dehkordi SR, Roudbar MA, Sargolzaei M, Guity K, Sedaghatikhayat B, et al. GWAS findings improved genomic prediction accuracy of lipid profile traits: tehran Cardiometabolic Genetic Study. Sci Rep 2021;11:5780. https://doi.org/10.1038/s41598-021-85203-8.
[56] Li TY, Zhang C, Asselbergs FW, Qi L, Rimm E, Hunter DJ, et al. Interaction between dietary fat intake and the cholesterol ester transfer protein TaqIB polymorphism in relation to HDL-cholesterol concentrations among US diabetic men. Am J Clin Nutr 2007;86:1524–9. https://doi.org/10.1093/ajcn/86.5.1524.
[57] Trajkovska KT. High-density lipoprotein metabolism and reverse cholesterol transport: strategies for raising HDL cholesterol. Anatol J Cardiol 2017. https://doi.org/10.14744/AnatolJCardiol.2017.7608.
[58] Abbey M, Nestel PJ. Plasma cholesteryl ester transfer protein activity is increased when trans-elaidic acid is substituted for cis-oleic acid in the diet. Atherosclerosis 1994;106:99–107. https://doi.org/10.1016/0021-9150(94)90086-8.
[59] Tahir A, Martinez PJ, Ahmad F, Fisher-Hoch SP, McCormick J, Gay JL, et al. An evaluation of lipid profile and pro-inflammatory cytokines as determinants of cardiovascular disease in those with diabetes: a study on a Mexican American cohort. Sci Rep 2021;11:2435. https://doi.org/10.1038/s41598-021-81730-6.
[60] Bernardi S, Marcuzzi A, Piscianz E, Tommasini A, Fabris B. The complex interplay between lipids, immune system and interleukins in cardiometabolic diseases. Int J Mol Sci 2018;19:4058. https://doi.org/10.3390/ijms19124058.
[61] Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev 2019;40:537–57. https://doi.org/10.1210/er.2018-00184.