Prevalence and factors associated with possible cases of familial hypercholesterolemia in Brazilian adults: a cross-sectional study

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Article

Keywords: Familial Hypercholesterolemia, Hyperlipoproteinemia type II, Cholesterol, LDL, Health surveys, Risk factors, Laboratory test, Cross-Sectional Studies, Brazil

Posted Date: April 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1547539/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on November 22nd, 2023. See the published version at https://doi.org/10.1038/s41598-023-47692-7.

Abstract

This study aimed to estimate the prevalence of possible cases of FH and analyze associated factors in the adult Brazilian population. Cross-sectional study with laboratory data from the Brazilian National Health Survey, with 8,521 participants. Possible cases of FH were defined according to the Dutch Lipid Clinic Network criteria. The prevalence and 95% confidence intervals (95%CI) of possible cases of FH were estimated according to sociodemographic variables, lifestyle, diabetes, hypertension, altered tests, treatment and self-rated health. Logistic regression was used to analyze the associations. The prevalence of possible cases of FH was 0.96%, higher in women, between 45 and 59 years, white race/skin color and others, less education, people with diabetes, hypertension and total cholesterol ≥ 310 mg/dL. The presence of FH was positively associated with regular self-rated health (OR 1.96; 95%CI 0.99–3.84), poor/very poor (OR 3.02; 95%CI 1.30–7.03) and negatively with black race/skin color (OR 0.10; 95%CI 0.02–0.46) and complete elementary school, incomplete high school (OR 0.47; 95%CI 0.23–0.98) and complete high school and more (OR 0.45; 95%CI 0.21–0.95). FH affects 1:104 Brazilian adults, these findings contribute to mitigate the burden of disease. Due to the scarcity of studies on FH in low- and middle-income countries, further studies are desirable.

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism. The occurrence of FH is due to mutations in the gene of low-density lipoprotein (LDLR), alloprotein B (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9) gene[1,2]. Approximately 95% of FH cases are due to LDLR mutations, with decreased or lost function[3].

FH is characterized by elevated total cholesterol (TC), very high low-density lipoprotein (LDL-Cholesterol) levels, tendinous xanthomas and corneal arch[1,2]. Considered severe due to the increased risk of premature coronary artery disease (CAD)[1,2], it is responsible for 5–10% of cardiovascular events under the age of 50[1].

Inheritance of one or two pathogenic alleles conditions clinical phenotypes for FH, heterozygous (HeFH) and homozygous (HoFH)[4]. HeFH is the most common genetic dyslipidemia leading to premature CAD throughout life[3,4]. The prevalence in the world population varies between 1/200–250[3] and 1/500[1], corresponding to 14–34 million cases[3,6]. Diagnosis is based on LDL-Cholesterol values above 190 mg/dL for adults[1,3,5] and on family history of early CAD[1,5]. HoFH is rarer[1,5] (world-wide prevalence between 1/160.000–1/320,000 and can cause cardiovascular involvement from childhood, and many individuals develop CAD and die before the age of 30 LDL-Cholesterol levels are above 500 mg/dl[5], leading to cholesterol deposits in the tendons, skin and vascular tissues[1].

FH is a public health concern and meets the World Health Organization (WHO)[7] criteria for identifying population-based diseases for early diagnosis and treatment[6,7], aiming to reduce cardiovascular

mortality in the population general[1].

The identification can be made by analyzing the lipid profile, determining TC and LDL-Cholesterol[1,3,5,7]. In this sense, some criteria have been proposed to standardize FH diagnosis, such as the Dutch Lipid Clinic Network (Dutch MEDPED) clinical score[1,3,5,7]. The Brazilian FH Directive[1] recommends using the Dutch MEDPED for simplicity of application, although a validation for the Brazilian population is not yet available[1].

Despite all the negative repercussions of FH, the disease is globally underdiagnosed and undertreated[7,8], amplifying the burden of cardiovascular disease (CVD) in low- and middle-income countries[2,6]. The identification of FH is a challenge[5] because many countries do not have records with these observations[9]. Consequently, there has been an exacerbation of the social and economic burden related to this problem for society, governments and healthcare systems[1].

In Brazil, there is little information on the population diagnosis of FH[6]. Researches describe age, race, overweight and obesity as factors associated with FH [10,11], but studies in the country that identify these factors are scarce. This study advances by identifying, through laboratory tests of the Brazilian National Health Survey (PNS – *Pesquisa Nacional de Saúde*), the most extensive health survey in Brazil [1,2], possible cases of FH in adults. Considering the importance of early determination of FH to achieve a reduction in morbidity and mortality through guidelines and necessary therapeutic measures[13].

Thus, the aim of this study was to estimate the prevalence of possible cases of FH and analyze the associated factors in the adult Brazilian population.

Material And Methods

Study design

This is a cross-sectional study with data from laboratory tests of PNS between 2014 and 2015. The PNS is a nationwide, household-based survey conducted by the Brazilian Institute of Geography and Statistics in partnership with the Ministry of Health[14].

Sample, eligibility criteria and data collection

The PNS used a three-stage probabilistic sample and obtained records from 64,348 households and 60,202 adult respondents. To carry out the laboratory tests, a sub-sample collection of 25% of the census sectors surveyed was planned[12,14].

The sub-sample of PNS laboratory consisted of 8,952 people. There was a loss of 418 samples (insufficient material, hemolysis, sample loss) and in this study, children under 20 years old with LDL-Cholesterol below 150 mg/dL were excluded, due to the diagnostic possibility of FH being in adults from 20 years of age onwards. years with levels above 190 mg/dL[1] (n = 13). The study adopted post-

stratification weights according to sex, age, education and region, aiming to establish estimates for the Brazilian adult population[12]. The sample consisted of 8,521 participants.

Peripheral blood collections were performed at any time of day[15] following the protocol that does not require fasting for cholesterol measurement[5]. TC, LDL-Cholesterol and HDL-Cholesterol were collected in tubes with gel. The clot was retracted for 30 minutes and after centrifugation was performed and the samples were sent under refrigeration at 2 to 8ºC, with temperature control in the steps. These parameters were measured by an automated enzymatic/colorimetric method[15]. Further methodological details are available in other publications[12,14,15].

FH definition

FH was defined according to the diagnostic criteria of the Dutch MEDPED[1,7] adapted[16], using the information available in the PNS database and based on population studies[10,11,17,18].

The Dutch MEDPED[1,7] score classifies FH into three categories: certainty above 8 points, probable 6 to 8 points and possible 3 to 5 points, according to the diagnostic criteria below:

a) Family history: first-degree relative with premature coronary/vascular disease (male < 55 years and woman < 60 years) or adult first- or second-degree relative with TC > 290 mg/dL (1 point); first-degree relative with tendon xanthoma and/or corneal arch or first-degree relative 260 mg/dL (2 points);

b) Clinical history: personal history of premature CAD (2 points); and/or premature cerebrovascular disease (1 point). Considering as premature, under 55 years old for men and under 60 years old for women;
c) Physical examination: xanthoma (6 points); corneal arch under 45 years old (4 points);
d) LDL-Cholesterol Levels (mg/dL): 155–189 (1 point), 190–249 (2 points), 250–329 (5 points), ≥ 330 (8 points);
e) DNA analysis (8 points).
Due to the variables collected in the PNS, in this study, LDL-cholesterol levels measured in the tests and history of premature CAD and/or stroke evaluated by self-reported diagnosis in the PNS questionnaire were used.

Possible cases of FH were defined using the following Dutch MEDPED score criteria[1,7]:

Criterion 1 (laboratory):

Assessed by LDL-Cholesterol ranges only. A dichotomous analysis was performed with or without FH at the cut-off point of 3 to 5 points, calculated by LDL-Cholesterol levels (mg/dL): 155–189 (1 point); 190–249 (3 points); 250–329 (5 points); ≥330 (8 points). Possible cases of FH were considered as LDL-Cholesterol levels ≥ 190 mg/dL, reaching 3 to 5 points in the score[1,7].

Criterion 2 (laboratory plus premature CAD and/or stroke):

Assessed by LDL-cholesterol ranges and self-report of premature CAD and/or stroke. The dichotomous analysis was performed with or without FH by the cut-off point of 3 to 5 points, calculated by: LDL-Cholesterol levels (mg/dL): 155–189 (1 point), 190–249 (3 points), 250–329 (5 points) and ≥ 330 (8 points); Premature CAD (2 points) and/or premature stroke (1 point), in men under 55 years and women under 60 years. Possible cases of FH were considered when reaching 3 to 5 points in the score[1,7].

Variables

This study included variables related to possible cases of FH, sociodemographic, lifestyle, additional risk factors for CVD, altered laboratory tests, treatment and health self-assessment. To construct the variables, questionnaires on lifestyles and chronic diseases and laboratory tests measured by the PNS were used. The questions used in the construction of the variables are shown in Table 1(supplementary material).

Table 1
– Prevalence of possible cases of FH and 95%CI in adults by criteria according to sociodemographic characteristics, Brazilian National Health Survey, Brazil, 2014–2015

		Possible cases of FH by criterion 1			Possible cases of FH by criterion 2		
		(3–5 points)			(3–5 points)		
		(n = 66)			(n = 87)		
Variables	**n**	**%**	**95%CI**	**p**	**%**	**95%CI**	**p**
Total	8,521	0.69	0.50–0.94		0.96	0.73–1.26	
Sex	8,521						
Male		0.46	0.27–0.78	0.043	0.67	0.41–1.08	0.043
Female		0.89	0.60–1.32		1.22	0.87–1.70	
Age							
20 to 29		0.47	0.15–1.45	0.044	0.49	0.16–1.45	0.004
30 to 44		0.32	0.18–0.56		0.49	0.24–0.97	
45 to 59		0.92	0.53–1.60		1.74	1.17–2.57	
60 years and older		1.13	0.70–1.85		1.13	0.69–185	
Race/skin color	8,521						
White and others		0.91	0.60–1.40	0.012	1.13	0.77–1.66	0.055
Black		0.052	0.007–0.37		0.14	0.03–0.61	
Brown		0.56	0.36–0.88		0.94	0.62–1.26	
Region	8,521						
North		0.68	0.40–1.15	0.771	0.86	0.54–1.35	0.714

The category not having FH was used to calculate the prevalence, but it is not shown in the table. FH: familial hypercholesterolemia. 95%CI: 95% confidence interval.

		Possible cases of FH by criterion 1			Possible cases of FH by criterion 2		
Northeast		0.64	0.42–0.97		0.83	0.57–1.20	
Southeast		0.69	0.37–1.27		0.92	0.54–1.55	
South		0.60	0.28–1.28		1.224	0.63–2.37	
Center-West		1.05	0.57–1.92		1.21	0.69–2.11	
Education	8,521						
Illiterate/Incomplete elementary school		1.08	0.74–1.57	0.019	1.55	1.10–2.17	0.002
Complete elementary school/incomplete high school		0.46	0.22–0.95		0.62	0.34–1.13	
Complete high school and more		0.43	0.21–0.88		0.58	0.31–1.06	

The category not having FH was used to calculate the prevalence, but it is not shown in the table. FH: familial hypercholesterolemia. 95%CI: 95% confidence interval.

Outcome variable

For analysis of associated factors, possible cases of FH defined by criterion 2 were used as the outcome variable.

Explanatory variables

Sociodemographic:

Gender (male and female); age (≥ 20 years old); Education (illiterate and incomplete elementary school, complete elementary school and incomplete high school, complete high school and more); Race/skin color (white and others that corresponded to yellow and indigenous; black; brown); Regions of Brazil (North, Northeast, Southeast, South and Center-West).

Lifestyle:

Overweight or obesity: classified by body mass index (BMI), as normal/underweight (BMI < 25 kg/m^2), overweight (BMI between 25 to 29 kg/m^2) and obesity (BMI ≥ 30 kg/m^2)[19]. Calculated by measured weight and height; Sufficient physical activity (PA) in free time (yes; no): the practice of 150 minutes per week of PA of light or moderate intensity, or at least 75 minutes per week of vigorous intensity, was considered active, regardless of the number of days of practice per week[20]; Consumption of red meat

with fat (yes; no); Binge drinking (yes; no): defined by the concept of “binge drinking”[21] (minimum consumption of 4 doses for women and 5 doses for men on a single occasion); Smoking (yes; no): positive responses to the use of tobacco products were considered as smokers.

Health self-assessment:

Categorized as very good/good, regular and very poor/poor.

Other variables included in the study

Additional risk factors for CVD:

Diabetes (yes; no): glycated hemoglobin values ≥ 6.5%[22] and self-reported diagnosis were considered; Hypertension (yes; no): Self-reported diagnosis and blood pressure measurements were used, considering values ≥ 140/90 mmHg[23].

Altered laboratory tests:

TC ≥ 310 mg/dL (yes; no); HDL ≤ 40 mg/dL (yes; no).

Treatment report:

Report of antihypertensive treatment (yes; no); Lipid-lowering treatment report (yes; no).

Statistical analyses

Prevalence was estimated as proportions (%) and 95% confidence intervals (95%CI) for LDL-Cholesterol levels according to Dutch MEDPED[1,7] according to sociodemographic characteristics; and for possible cases of FH according to criteria 1 and 2 according to sociodemographic characteristics, additional risk factors for CVD, altered laboratory tests, treatment report, lifestyle and health self-assessment. Bivariate analyzes were performed using the chi-square test, with a significance level of 5% ($p \leq 0.05$).

To analyze the associations between the outcome and explanatory variables, the logistic regression model was applied and the Odds Ratio (OR) and 95%CI were calculated. For the bivariate analyses, the crude ORs (cOR) were estimated. In the multivariate analysis, the variables that presented a p-value < 0.20 were included in the bivariate analyzes and the adjusted ORs (aOR) were estimated. In the final model, the variables that presented a p-value ≤ 0.05 were considered as associated factors.

Data Analysis and Statistical Software (Stata) version 14 was used, using the survey module that considers post-stratification weights.

The dataset is available in the PNS repository (www.pns.fiocruz.br). The PNS was approved by National Committee of Ethics in Research, Ministry of Health, under Opinion 328,159. Participation was voluntary and the confidentiality of information guaranteed.

Results

The prevalence of LDL-Cholesterol by range Dutch MEDPED, for levels (mg/dL) between: 155–189 was 4.84%; 190–249 was 0.64%; and 250–329 was 0.044%. Nine people with LDL-Cholesterol levels between 155–189 had premature CAD and one person with levels between 190–249 had premature stroke (data not shown) (Supplementary Table 2).

The prevalence of possible cases of FH according to criterion 1 was 0.69%, 0.89% in women, 0.91% in white race/color and others, 1.13% in those aged 60 years and over and 1.08% in the least educated. The prevalence of possible cases of FH by criterion 2 was 0.96%, 1.22% in women, 1.74% between 45 and 59 years old, 1.13% in white race/color and others and 1.55% in the less educated (Table 1).

The prevalence of possible cases according to criterion 1 was higher in people with diabetes (1.33%) and TC ≥ 310 mg/dL (59.95%). According to criterion 2, the prevalence of possible cases of FH was higher in people with hypertension (1.75%), diabetes (1.85%) and TC ≥ 310 mg/dl (59.95%), 3.29% reported taking lipid-lowering treatment and 1.62% anti-hypertensive treatment, however, without statistically significant differences ($p > 0.05$) (Supplementary Table 3). In supplementary table 4, the prevalence of possible cases according to criterion 1 is presented, according to selected variables (sociodemographic, lifestyle and health self-assessment).

By criterion 2, in the bivariate analysis, being female (cOR 1.84; 95%CI 1.01–3.36), aged between 45 and 59 years (cOR 3.59; 95%CI 1.12–11.48) and health self -regular assessment (cOR 2.31; 95%CI 1.25–4.30) and poor/very poor (cOR 3.94; 95%CI 1.79–8.70) were positively associated with FH. Being of black race/color (cOR 0.13; 95%CI 0.03–0.56), complete elementary school and incomplete high school (cOR 0.39; 95%CI 0.20–0.79), complete elementary school and incomplete high school (cOR 0.39; 95%CI 0.20–0.79) or complete high school and more (cOR 0.37; 95%CI 0.18–0.75) and practice PA (cOR 0.42; 95%CI 0.17–0.84) were negatively associated with FH (Table 2).

Table 2
– Prevalence and factors associated with possible cases of FH by criterion 2 in adults according to variables selected, Brazilian National Health Survey, Brazil, 2014–2015

		Possible cases of FH by Criterion 2 (n = 87)				
Variables	**n***	**%**	**95%CI**	**cOR**	**95%CI**	**p****
Total	8,521	0.96	0.73–1.26			
Sex	8,521					
Male		0.67	0.41–1.08	1		0.046
Female		1.22	0.87–1.70	1.84	1.01–3.36	
Age	8,521					
20 to 29		0.49	0.16–1.45	1		
30 to 44		0.49	0.24–0.97	0.99	0.27–3.63	0.99
45 to 59		1.74	1.17–2.57	3.59	1.12–11.48	0.031
60 years and older		1.13	0.69–185	2.32	0.70–7.71	0.17
Race/skin color	8,521					
White and others		1.13	0.77–1.66	1		
Black		0.14	0.03–0.61	0.13	0.03–0.56	0.007
Brown		0.94	0.62–1.26	0.83	0.47–1.45	0.507
Region	8,521					
North		0.86	0.54–1.35	1		
Northeast		0.83	0.57–1.20	0.97	0.53–1.76	0.913

*Missing data not presented. The category not having FH was used to calculate the prevalence, but it is not shown in the table. FH: familial hypercholesterolemia. 95%CI: 95% confidence interval. cOR: Crude Odds Ratio. **p value of cOR.

		Possible cases of FH by Criterion 2 (n = 87)				
Southeast		0.92	0.54–1.55	1.07	0.53–2.17	0.842
South		1.224	0.63–2.37	1.43	0.63–3.24	0.385
Center-West		1.21	0.69–2.11	1.42	0.68–2.95	0.35
Education	8,521					
Illiterate/Incomplete elementary school		1.55	1.10–2.17	1		
Complete elementary school/incomplete high school		0.62	0.34–1.13	0.39	0.20–0.79	0.009
Complete high school and more		0.58	0.31–1.06	0.37	0.18–0.75	0.006
Body Mass Index	8,429					
Low/Normal		0.74	0.44–1.23	1		
Overweight		1.19	0.79–1.78	1.62	0.84–3.12	0.153
Obesity		0.97	0.53–1.77	1.32	0.59–2.92	0.500
Physical activity	8,511					
No		1.11	0.82–1.49	1		0.016
Yes		0.42	0.20–0.88	0.38	0.17–0.84	
Consumption of red meat with fat	8,041					
No		1.08	0.79–1.48	1		0.373
Yes		0.79	0.43–1.46	0.73	0.37–1.46	
Binge drinking	8,521					

*Missing data not presented. The category not having FH was used to calculate the prevalence, but it is not shown in the table. FH: familial hypercholesterolemia. 95%CI: 95% confidence interval. cOR: Crude Odds Ratio. **p value of cOR.

		Possible cases of FH by Criterion 2 (n = 87)				
No		0.97	0.72–1.29	1		0.900
Yes		0.91	0.37–2.20	0.94	0.37–2.42	
Smoking	8,514					
No		0.87	0.64–1.18	1		0.156
Yes		1.45	0.77–2.17	1.67	0.82–3.40	
Health self-assessment	8,514					
Very good/good		0.62	0.40–0.97	1		
Regular		1.42	0.93–2.16	2.31	1.25–4.30	0.008
Very poor/poor		2.40	1.26–4.50	3.94	1.79–8.70	0.001

*Missing data not presented. The category not having FH was used to calculate the prevalence, but it is not shown in the table. FH: familial hypercholesterolemia. 95%CI: 95% confidence interval. cOR: Crude Odds Ratio. **p value of cOR.

By criterion 2, in the multivariate analysis, regular health self-assessment (aOR 1.96; 95%CI 0.99–3.84) and poor/very poor (aOR 3.02; 95%CI 1.30–7.03) were associated with if positively to FH. On the other hand, having completed elementary school and incomplete high school (aOR 0.47; 95%CI 0.23–0.98) or having completed high school and more (aOR 0.45; 95%CI 0.21–0.95) and being of black race/color (aOR 0.10; 95%CI 0.02–0.46) were negatively associated with FH (Table 3).

Table 3
Factors associated with possible cases of FH by criterion 2 in Brazilian adults, Brazilian National Health Survey, Brazil, 2014–2015

Variable	aOR	95%CI	p**
Education			
Illiterate/Incomplete elementary school	1		
Complete elementary school/incomplete high school	0.47	0.23–0.98	0.044
Complete high school and more	0.45	0.21–0.95	0.036
Race/skin color			
White and others	1		
Black	0.10	0.02–0.46	0.003
Brown	0.72	0.42–1.23	0.228
Health self-assessment			
Very good/good	1		
Regular	1.96	0.99–3.84	0.050
Very poor/poor	3.02	1.30–7.03	0.010

FH: familial hypercholesterolemia. 95%CI: 95% confidence interval. aOR: Adjusted Odds Ratio (Final Model). **P-value of aOR.

Discussion

This study identified the prevalence of possible cases of FH and associated factors in a representative sample of Brazilian adults. The frequency of FH in adults in Brazil was 1 case in 104 individuals, affecting more women, those aged 45 to 59 years, less educated, with TC ≥ 310 mg/dL, hypertension and diabetes. The presence of FH, regular and very poor/poor health self-assessment, and negatively associated with higher education and black race/color were positively associated. The early identification of individuals with FH is relevant as it can enable early treatment with statins, capable of reducing cardiovascular events in these individuals by up to 76%[25].

In this study, the prevalence of possible cases of FH was higher than that estimated in a meta-analysis that found 0.40% (frequency of 1:250)[9] and in relation to the Elsa-Brazil study that identified 0.40% (1:263)[11]. Studies have identified the following prevalence of FH in adults: 0.40% in the United States (1:250)[17], 0.30% in China (1:256)[10], 0.85% in France (1:120)[18] and 0.73% in Denmark (1:137)[26], and the frequency in this study approached these last two countries[18,26].

The high FH prevalence values found in this study may be influenced by not excluding secondary causes, such as hypothyroidism and nephrotic syndrome[1]. The exclusion of secondary causes was not possible due to the lack of information in the PNS. Also the absence of genetic testing[1], although not mandatory in case of unavailability[1,24], may have contributed to the inclusion of other dyslipidemias or metabolic diseases that lead to lipid alterations[1,5]. It is noteworthy that although we used the adapted Dutch MEDPED criteria, individuals diagnosed with FH by criterion 2 are more likely to have severe hypercholesterolemia by behavioral and non-genetic causes, a possibility that can be corroborated by the higher prevalence of other metabolic alterations in this group when compared by criterion 1. However, considering that early diagnosis and treatment in FH reduce unfavorable clinical outcomes[1], it was decided to maintain more sensitive criteria, even losing in specificity.

Studies show that men and women can be equally affected by FH[1,27]. However, we identified a higher prevalence in women, as in Poland[28], Catalonia[29] and China[10]. There is evidence of gender disparities in FH treatment, with the disease having a different weight in women, with implications for treatment adherence[30]. Women are less likely to use statins and to discontinue therapy, and consequently may not reach recommended LDL-cholesterol levels[30]. The reasons are related to the challenges faced in the childbearing age regarding the choice of contraceptives and lipid-lowering therapy; discontinuation of treatment with lipid-lowering drugs because they are teratogenic during pregnancy, a phase in which LDL-Cholesterol levels are increased in FH; choice of therapy or restart during breastfeeding; and menopausal care in women with FH, in which LDL-Cholesterol levels are higher compared to men[30]. Another possible explanation is due to survival bias related to early and fatal manifestations of FH in men[11].

Regarding race/color, the result of this investigation diverges from the Elsa-Brazil Study, in which FH affected more browns and blacks[11], while a study in the United States identified higher prevalence in whites[17]. Another study in Brazil with laboratory data from the PNS identified lower prevalence of high LDL-Cholesterol in blacks and browns[31]. Possible justification is due to the adopted score[1,3,5,7], which uses LDL-Cholesterol in its algorithm[1,3,5,7]. There is no consensus in the literature regarding the genetic factors that allow predicting the highest prevalence of FH in certain ethnic-racial groups[32]. There is little information about FH in mixed-race populations[11], making further research in the country necessary, especially due to miscegenation of Brazilians.

With regard to the relationship of FH with age, a decrease in LDL-Cholesterol levels in FH is expected with advancing years[18]. However, in this study, the prevalence increased with age, as in studies in French[18], Chinese[10], Danish[26] and Elsa-Brasil[20]. In the present investigation, as in others that adopted part of the score[10,11,17,18,26], the prevalence was lower in young people[10,11,26]. However, this also occurred in research with more complete scoring algorithms, which included, in addition to LDL-Cholesterol levels and a history of premature CAD and stroke[10,11,17,18,26], family history[10,11,18,26] and/or genetic test[26]. Although this phenomenon may be attributable to not using all the score criteria, it implies that FH is underdiagnosed in young people, as it is a genetic condition[26]. On the other hand, not excluding

secondary causes may have increased patients with severe metabolic disorders[1], and contributed to overestimating the prevalence of FH at older ages, when secondary causes are more prevalent[4].

This study showed a negative association between higher education and the presence of FH. This finding is relevant as adults with FH who have low education are less likely to seek health care, adhere to treatment and advocate for tracking relatives[33,34]. Patients with FH with low education benefit, therefore, from educational interventions about the disease, constituting important tools for FH control, treatment and tracking among index cases[33,34].

Another interesting association was the presence of FH in adults with worse self-rated health. A study with data from PNS showed a strong association between poor health self-assessment and dyslipidemias[35]. Health self-assessment is a predictor of morbidity and mortality and use of health services[35,36]. It expresses individuals' social, psychological and biological dimensions and is related to a greater understanding of the diagnosis, symptoms, decreased functionality and risk of mortality[35,36]. Possible justifications for these findings can be explained by participants' perception of the severity and risks[36] of FH.

People with diabetes, hypertension and TC ≥ 310 mg/dL had higher prevalence of possible cases of FH, conditions that further increase the risk of CVD in the presence of FH[1,37]. In people with FH, diabetes increases the risk of CVD by 2.19-fold37 and hypertension confers the 1.4-fold greater risk of CVD[37]. Thus, it is important to emphasize to individuals with FH the relevance of diagnosis and adoption of treatment for these conditions[1,37]. Very increased TC values may be indicative of FH and excluding secondary dyslipidemias, these adults should be evaluated for the possibility of the disease[1,24].

This study had as limitations: the impossibility of attesting a causal relationship. Associations can reflect lifestyle and treatment. The inexistence of all the score criteria and the impossibility of excluding secondary causes of dyslipidemia, due to the unavailability of information in the PNS base, may have underestimated or overestimated the prevalence. Some results may be subject to survival bias and reverse causality, and should be carefully evaluated. However, in Brazil there is little information about FH[6–8]. So far, in the only previous population study found, the sample composed of employees of Brazilian public universities[11]. Although we do not have the exact and robust conditions for defining the disease by the full score, this study allowed us to estimate, for the first time, possible cases of FH and associated factors in a representative sample of Brazilians, approaching the reality of the country and in line with WHO efforts[7].

Furthermore, the results imply the importance of introducing an early and systematic FH screening program in the country[8]. It is worth mentioning that FH diagnosis, in case of unavailability of the genetic test, should be based on LDL-Cholesterol levels and on family tracking of confirmed index cases[1,29]. Knowing the lipid profile helps to diagnose a greater number of cases[1], given that the chances of other

carriers from the index case are 50% in first-degree relatives, 25% in second-degree and 12.5% in third-degree[38].

Moreover, the identification of high LDL-Cholesterol levels, regardless of FH diagnosis, is relevant, given that these individuals are at increased risk of morbidity and mortality from CVD and should be evaluated for the presence of secondary causes or indication of lipid-lowering treatment, according to the risk cardiovascular[39]. One fifth of Brazilian adults have high LDL-Cholesterol[31], which constituted only in 2019, in Brazil, as the eighth cause of loss of disability-adjusted life years (DALYs), causing 2,363,140 million DALYs (3.62% of the total) and the sixth cause of deaths, causing 99,375 deaths (7.04% of the total)[40].

Conclusions

The frequency of possible cases of FH in adults in Brazil was 1:104. FH were negatively associated with being of black race/color and with higher education, and positively associated with regular health self-assessment, poor/very poor. The study showed that there was an increase in prevalence when estimating by more score criteria, showing that the inclusion of other score information can identify more individuals with FH. Diagnosis of possible cases of FH can help reduce the impact on cardiovascular morbidity and mortality in Brazilians by enabling early treatment, and are in line with WHO efforts to identify FH in low- and middle-income countries for CVD prevention.

Declarations

Acknowledgments

We would like to thank the Coordination for the Improvement of Higher Education Personnel (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) for the PhD scholarship received by ACMGNS; the Brazilian National Council for Scientific and Technological Development (CNPq - *Conselho Nacional de Desenvolvimento Científico e Tecnológico*) for the Research Productivity grant received by DCM; the support received from the Graduate Program in Nursing at UFMG with resources from PROAP/CAPES; the Ministry of Health's Health Surveillance Department for funding - TED 147/2018; Pedro Cisalpino Pinheiro for his support in statistical data treatment.

Authors' contributions: ACMGNS participated in the conception, design, analysis, data interpretation and writing of the article. CSG and EJSP participated in the analysis, data interpretation and writing of the article. LCCB and DCM participated in the design, data interpretation and review of the article. All authors approved the final version of the manuscript.

Data availability statement: The datasets generated during and/or analyzed during the current study are available in the Institute of Communication and Scientific and Technological Information in Health of Oswaldo Cruz Foundation (Icict/Fiocruz, in portuguese) repository, https://www.pns.icict.fiocruz.br/bases-de-dados/.

Competing interests: The author(s) declare no competing interests.

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