

The Independent Association Between Age and Serum Cholesterol Levels in Patients with Familial Hypercholesterolemia

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Research Article

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Abstract

(1) Background: Studies have suggested that age and the serum total cholesterol (TC) concentration are independent risk factors for cardiovascular disease (CVD) in patients with familial hypercholesterolemia (FH); however, the relationship between age and TC in patients with FH is unclear. We aimed to investigate the correlation between age and TC in patients with FH.

(2) Methods: In this retrospective, controlled not matched analysis, a total of 103 patients with FH and 106 non-FH controls were recruited into the study from 2004 to 2017. Spearman and partial correlation analyses, as well as multiple regression analyses, were used to evaluate the relationship between TC and age.

(3) Results: There were no significant differences in age, gender, or BMI between the FH group and the control group ($p > 0.05$). Family history of CVD, TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein (a) (Lp(a)) and non-HDL-C levels were significantly higher in patients with FH compared to the control ($p < 0.01$). Additionally, the serum TC levels for ages ≥ 50 years were significantly higher than those for ages < 50 years ($p < 0.05$) in FH patients. In both Spearman and partial correlation analyses, age was found to be significantly correlated with serum TC ($p < 0.001$) in the FH group but not in the control group, which was confirmed by further multiple linear regression analyses and logistic regression analyses.

(4) Conclusions: Age is an independent factor influencing serum TC level in patients with FH, and it is necessary to conduct early screening and early intervention.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal, co-dominant disorder caused by mutations in the low-density lipoprotein receptor gene, which causes the dysmetabolism of circulating, low-density lipoprotein cholesterol (LDL-C), thus maintaining it at a high level [1, 2]. Hypercholesterolemia is known to cause atherosclerotic plaque formation in blood vessel walls, which puts patients with hypercholesterolemia at high risk of atherosclerotic disease (ASCVD), including coronary heart disease (CHD). The prevalence of the disease in patients with heterozygous FH is estimated to be 1 in 300 to 1 in 500. Based on this estimate, approximately 10 million people worldwide have FH, which is characterized by severe elevated serum cholesterol (TC) levels and xanthoma [3, 4]. A survey of the current situation of FH in China shows that the prevalence of FH in the Chinese population is similar to that in other countries; however, FH is mainly found in patients with early-onset CHD in China, which is characterized by poor control of lipid levels and a higher risk of cardiovascular disease (CVD) [5].

The longer patients survive with extremely high levels of LDL-C due to being born with defective LDL receptors, the higher their risks of developing CVD will be. Therefore, many studies have emphasized the importance of the early identification of FH for the early prevention of CVD [6-9]. So far, some large cohort studies have identified age and other factors as independent risk factors for CVD in FH patients, and

some existing formulas for predicting the risk of CVD events in FH patients, such as Montreal-FH-SCORE (MFHS), Framingham risk score (FRS), SAFEHEART risk equation, etc., have been combined with clinical variables including age [10-13]. Thus, it can be seen that age is an independent risk factor for CVD in FH patients.

Although age is a risk factor for CVD in patients with FH, we suspect that this is determined by the association between age and lipid levels—that is, with increasing age, the levels of some serum lipids (mainly TC, LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), etc.) also increase, which leads to a higher risk of CVD events. Recently, Schienkiewitz A et al. published a study on the association between age and serum lipid levels in children and adolescents[14], while the association between age and serum lipid levels in FH families remains unclear. Thus, we conducted a case–control study to provide additional insights into the relationship between age and serum cholesterol in patients with FH to support the early recognition and early treatment of FH.

2. Materials And Methods

2.1. Study population

The FH study samples were initially screened from the database of the project "Hyperlipidemia Family Blood Sample Collection and Clinical and Genetic Epidemiology research", which belongs to the Chinese "National High Technology Research and Development Program" ("863 Project"). Then, according to the diagnostic criteria of the Dutch Lipid Clinic Network (DLCN) [15], patients with a score of 6 or more (namely, the definite FH or probable FH samples) were included in the study. Since 2020, we conducted this study after accessing to information that could identify individual participants during or after data collection.

The following is a brief introduction to the "Hyperlipidemia Family Blood Sample Collection and Clinical and Genetic Epidemiology research": The screened individuals had visited the outpatient Lipid Clinic from the First Hospital of Lanzhou University from 2004 to 2017. Based on their fasting blood lipid levels, they were invited to be examined again along with their first-degree relatives on an arranged date. On this arranged date, the following were performed and recorded: serum lipid level and other biochemical detections, a medical physical check-up, and a face-to-face questionnaire survey. The signed informed consent of each patient was also obtained. A subject was recruited into the program if they met two of the following three criteria: 1) At least two members in their pedigree had dyslipidemia as defined by the American National Cholesterol Education Program (NCEP ATP III) [16], which means that their TC levels ≥ 6.20 mmol/L and/or LDL-C levels ≥ 4.10 mmol/L, with no secondary cause; 2) at least two generations in their pedigree were affected; 3) at least one hypercholesterolemic member in their pedigree was affected and their onset age was ≤ 50 years.

In addition, 106 samples were selected from the project database for the control group as the database also included data from normal families who participated in the health examination. Patients in the

control group ranged in age from 18 to 85 years and did not have severe liver, kidney, or heart dysfunction; thyroid disease; systemic inflammation; or malignant tumors.

Sample size calculation of linear correlation analysis was shown in Formula 1. And in current study, the bilateral $\alpha = 0.05$, $u_{0.05/2} = 1.96$; $\beta = 0.1$, $u_{0.1} = 1.282$.

$$n = 4 \left[\frac{(u_{\alpha} + u_{\beta})}{\ln \left(\frac{1+r}{1-r} \right)} \right]^2 + 3 \quad (1)$$

Note: in the formula, n is the minimum sample size required, u_{α} and u_{β} are u values corresponding to test level α and type II error probability β , respectively, and r is an estimate of the overall correlation coefficient.

2.2. Clinical assessment

Body mass index (BMI) is the weight (kg) of a person divided by the square of their height (m²). A family history of CHD is considered if a first-degree relative (males < 55 yrs; females < 60 yrs) has a history of CHD. In our study, CHD was diagnosed by the presence of at least 50% obstructive stenosis of any of the main coronary arteries by coronary angiography. Xanthoma included tendinous xanthoma (which could be located the back of the fingers, elbows, knees, or elsewhere and also included the thickening of the Achilles tendon) and tuberous xanthoma, as well as rash and flat xanthoma. A repeated measurement of fasting blood glucose (FBG) level ≥ 7.0 mmol/L or hypoglycemic treatment was identified as diabetes mellitus (DM). Hypertension (HT) was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg measured at least twice, or as taking anti-hypertensive drugs. Mean arterial pressure (MAP) was calculated by $(SBP + 2*DBP)/3$. Patients who had smoked regularly for the past 3 months were considered current smokers, and those who had quit smoking and had not smoked for more than 1 year were considered non-smokers. Those who drank every month or had drunk for more than six months were considered current drinkers. In this study, lipid-regulating drugs mainly included statins and some proprietary Chinese medicines, such as Zhibituo, Gynostemma, and Ginkgo biloba.

2.3. Laboratory determination

After fasting for 8 to 12 hours, blood was collected from the cubital vein in the morning of the following day. After centrifugation at 3000 rpm at 4 °C for 10 minutes, serum was collected and stored at -80 °C for detection. Serum lipid and other biochemical items including TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and FBG were measured by an automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA). Serum concentrations of TC, HDL-C, LDL-C, and TG were determined by enzyme colorimetry, and the levels of apolipoprotein A1 (apoA1), apolipoprotein B (apoB), and lipoprotein

(a) (Lp(a)) were determined by immunoturbidimetry according to the manufacturer's specifications. The value of non-HDL-C was obtained by subtracting the value of HDL-C from the value of TC.

2.4. Statistical analysis

Data were analyzed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA). Compliance of data with the normal distribution was assessed by Kolmogorov–Smirnov One–Sample Test. For continuous variables, the normal distribution was represented by the mean \pm standard deviation (SD), and the non-normal distribution was represented by the median (25%-75%). Categorical variables were expressed as a number (percentage). Spearman correlation analysis and sex-adjusted partial correlation analysis were used for the correlation between TC and related clinical parameters. Continuous variables were analyzed using the Student's t-test, Mann–Whitney U test, or variance (ANOVA) analysis, and categorical variables were assessed using the chi-square test to evaluate the differences in clinical characteristics and biochemical parameters between groups. Multiple linear regression analysis and binary logistic regression analysis were used to determine whether age was an independent factor that influenced serum TC elevation in patients with FH. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 209 individuals (103 in FH and 106 in control group) were enrolled, with an average age of (48.12 ± 15.58) years, 41.1% male, and an average BMI of (23.35 ± 3.45) kg/m². The demographic and clinical characteristics of the patients with FH and the control group are shown in Table 1. The age range in the FH group and the control group was 18–85 years. There were no significant differences in age, gender, or BMI between the FH group and the control group ($p > 0.05$). It was observed that the FH group had a higher percentage of patients with a CHD-positive family history (66% vs. 17.9%, $p < 0.01$) and significantly higher levels of atherosclerotic lipids, including TC, LDL-C, apoB, Lp(a), and non-HDL-C than the control group ($p < 0.01$).

Table 1

Baseline characteristics of study population

3.2. Correlation analysis of TC with age and other relevant clinical parameters

As shown in Figure 1, the study population was divided into a group whose members were ≥ 50 years old

Variables	All	FH	Control	p
	n=209	n=103	n=106	
Age, years	48.12 ± 15.58	46.12 ± 14.29	50.06 ± 16.57	0.067
Male, N(%)	86(41.1%)	39(37.9%)	47(44.3%)	0.418
BMI, kg/m ²	23.35 ± 3.45	23.63 ± 3.39	22.63 ± 3.55	0.122
Familial history of CHD, N(%)	87(41.6%)	68(66%)	19(17.9%)	<0.001
Xathoma, N(%)	18(8.6%)	18(17.5%)	NA	NA
Lipid-regulating drugs, N(%)	12(5.7%)	12(11.7%)	NA	NA
DM, N(%)	13(6.2%)	4(3.9%)	9(8.5%)	0.283
HT, N(%)	53(25.4%)	28(27.2%)	25(24.3%)	0.550
Smoking, N(%)	59(28.2%)	28(27.2%)	31(29.2%)	0.741
Drinking, N(%)	84(40.2%)	45(43.7%)	39(36.8%)	0.309
FBG, mmol/L	4.99 ± 0.93	4.96 ± 0.79	5.01 ± 1.05	0.695
TC, mmol/L	5.10 ± 1.44	5.86 ± 1.41	4.36 ± 1.05	<0.001
LDL-C, mmol/L	3.38 ± 1.20	3.95 ± 1.30	2.84 ± 0.78	<0.001
TG, mmol/L	1.36(0.90–1.91)	1.48 (0.90–2.34)	1.31 (0.9–1.8)	0.142
HDL-C, mmol/L	1.24 ± 0.31	1.33 ± 0.27	1.17 ± 0.37	0.001
apoA1, g/L	1.39 ± 0.34	1.43 ± 0.27	1.34 ± 0.40	0.069
apoB, g/L	0.88 ± 0.24	0.93 ± 0.50	0.87 ± 0.24	0.680
Lp(a), mg/L	226(117–307)	249.5(168–309.2)	108(38.5–304)	0.007
non-HDL-C, mmol/L	3.86 ± 1.30	4.54 ± 1.32	3.21 ± 0.89	<0.001

Data are presented as mean ± SD, median (25th-75th percentile) or n (%). Bold values indicate statistical significance. FH, familial hypercholesterolemia; BMI, body mass index; CHD, coronary heart disease; DM, **diabetesmellitus**; HT, **hypertension**; FBG, Fasting blood glucose; TC, Total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; Lp(a), lipoprotein (a).

(elderly group) and a group whose members were < 50 years old (youth group). By comparing the concentration of the serum TC level between the two groups, we found that in patients with FH the serum TC level in the elderly group was significantly higher than that of the youth group ($p < 0.05$), while there were no statistical differences in the control group ($p > 0.05$). Spearman correlation analysis showed that age was significantly correlated with TC level in the FH group ($r = 0.351$, $p < 0.001$) but not in the control group ($r = -0.066$, $p = 0.504$), as shown in Figure 2. After adjusting for sex, the partial correlation analysis also showed that age was significantly correlated with TC in the FH group ($r = 0.488$, $p < 0.001$), but not in

the control group ($r = -0.076$, $p = 0.646$), as shown in Table 2. Meanwhile, the correlation between serum TC value and other important clinical parameters are also summarized in Table 2. The TC value between the FH group and the control group was also significantly correlated with several other atherosclerotic lipid indexes (LDL-C, apoB and non-HDL-C) ($p < 0.01$). Age, SBP, and FBG were found to be significantly correlated with the TC value in the FH group ($p < 0.01$), but not in the control group ($p > 0.05$).

Table 2

Correlation between TC and other cardiovascular risk factors after adjusting sex

Variables	TC–FH		TC–Control	
	r	p	r	p
Age, years	0.488	0.001	-0.076	0.646
BMI, kg/m ²	0.128	0.386	0.241	0.140
SBP, mmHg	0.286	0.049	-0.012	0.914
DBP, mmHg	0.137	0.355	-0.051	0.635
MAP, mmHg	0.209	0.153	-0.038	0.725
FBG, mmol/L	0.102	0.489	0.280	0.085
LDL-C, mmol/L	0.893	<0.001	0.969	<0.001
TG, mmol/L	0.225	0.124	0.273	0.093
HDL-C, mmol/L	0.525	<0.001	0.638	<0.001
apoA1, g/L	0.423	0.003	0.587	<0.001
apoB, g/L	0.760	<0.001	0.853	<0.001
Lp(a), mg/L	-0.125	0.398	0.395	0.013
non-HDL-C, mmol/L	0.979	<0.001	0.954	<0.001

Partial correlation analyses were used. Bold values indicate statistical significance. FH, familial hypercholesterolemia; TC, Total cholesterol; BMI, body mass index; SBP, **systolic pressure**; DBP, **diastolic pressure**; MAP, **mean arterial pressure**; FBG, fasting blood glucose; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; Lp(a), lipoprotein (a).

3.3. Age was an independent factor that influenced the elevation of serum TC in the FH group

In view of the above correlation in the FH group, multiple linear regression analysis was used to further determine the relationship between age and TC. By performing the stepwise procedure to the models, age was independently associated with the TC level after adjusting for sex, FBG, BMI, lipid-regulating drug use, xanthoma, smoking, alcohol consumption, CHD history, MAP and Lp(a) ($\beta = 0.042$, $p < 0.001$, Table 3). At the same time, we used the forward maximum likelihood method for multi-factor binary logistic regression analysis, and age was identified as an independent risk factor for increased TC in the FH group after adjusting for sex, DM, BMI, lipid-regulating drugs use, xanthoma, smoking, alcohol consumption, CHD history, MAP, and Lp(a). That is, compared with the youth group, the risk of serum TC ≥ 6.2 mmol/L was significantly higher in the middle-aged and elderly group (OR = 9.23 (2.32–36.68), $p < 0.01$), as shown in Table 4.

Table 3

Multiple linear regression analysis of the relationship between age and TC in FH

Models	Independent variable (Age)	
	β (unstandardized)	p
Crude	0.035	<0.001
1	0.040	0.001
2	0.042	<0.001

Multivariable stepwise linear regression models are shown. TC is the dependent variable. Model 1 adjusted for sex, FBG, BMI, lipid-regulating drugs use, xanthoma, alcohol consumption, history of CHD, MAP and Lp(a); Model 2 adjusted for confounders in model 1 plus smoking. TC, total cholesterol; FH, familial hypercholesterolemia; FBG, fasting blood glucose; BMI, body mass index; CHD, coronary heart disease; MAP, [meanarterialpressure](#); Lp(a), lipoprotein (a).

Table 4

Logistic regression analysis of age as a risk factor for changing serum TC level in FH

	Age < 50 yrs	Age ≥ 50 yrs	Crude OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)
TC < 6.2 mmol/L	26	3	1	1	1
TC ≥ 6.2 mmol/L	9	12	4.231 (1.802-9.934)	7.857 (2.201-28.053)	9.230 (2.323-36.680)
p			0.001	0.002	0.002
Model 1: Adjusted for hyperglycemia, overweight, using lipid-regulating drugs, xanthoma, smoking, drinking, history of CHD, MAP > 105 mmHg and Lp(a) ≥ 300 mg/L; Model 2: Adjusted for confounders in model 1 plus female. TC, total cholesterol; FH, familial hypercholesterolemia; CHD, coronary heart disease; MAP, mean arterial pressure ; Lp(a), lipoprotein (a).					

4. Discussion

According to the sample size estimation formula of linear correlation analysis (see Formula 1), and the correlation coefficient $r = 0.351$ between serum TC and age in FH patients obtained in this study, substituted into the formula, the theoretical sample size $n = 81$, our actual sample size $n = 103$. It can be seen that the sample size of this study has exceeded the minimum required sample size, indicating that this study can guarantee the reliability of the conclusion.

In fact, after analyzing the correlation between age and the serum TC level in the FH group, we also analyzed the correlation between age and the serum LDL-C level through Spearman correlation analysis, partial correlation analysis, and multiple regression analysis following the same path and obtained the same results. In other words, age was found to be an independent factor that influenced serum TC and LDL-C levels in the FH group. It is known that age is an independent risk factor for many diseases, including hypertension and a variety of tumor diseases, and with increasing age the incidence of various diseases gradually increases. By analyzing the relationship between serum TC level and age in FH families, the results of this study also showed a positive correlation that was consistent with our previous conjecture. Therefore, it is reasonable to believe that the serum cholesterol level, which has been proposed by previous studies to be an independent risk factor for the occurrence of CVD in patients with FH [17], would increase the exposure time (also age), accelerating the increases in CVD risk in patients with FH. Michael J Domanski et al. evaluated the relationship between the areas under the LDL-C and age curves and the risk of developing CVD in these patients using data from the Coronary Artery Risk Development Study in Young Adults. It was found that both the areas under the LDL-C and age curves and the time course of area accumulation were significantly correlated with the risk of a CVD event [18]. It can be seen that the risk of a CVD event depends on the time course of area accumulation. Therefore, this study has important implications for the control of TC and LDL-C in early life and the prevention of CVD in patients with FH. This was in line with the results of this study, which showed that the FH group had a higher family history of CHD than the control group.

Genotypes and phenotypes are the main causes of ASCVD in FH patients [17], and several vast cohort studies have confirmed that age is an independent risk factor for CVD in FH patients [10-13], while the results of this study indicate that age is an independent influencing factor for serum TC and LDL-C elevation in FH patients. The clinical significance of this study lies in the following points: On the one hand, the time accumulation effect of serum cholesterol reveals that age is an independent risk factor for ASCVD in FH patients; on the other hand, it is consistent with the spatial-temporal expression theory of genes for inherited diseases [19, 20]. That is, with an increase in age, the risk of disease gradually increases. In conclusion, early identification and the early application of cholesterol-regulating therapy should be encouraged to reduce the risk of temporal cumulative effects of serum cholesterol in patients with FH. At the same time, we should encourage the screening of blood lipid levels in those with abnormal blood lipids and pay more attention to the early identification of FH. In support of this, Lidewij et al. highlighted a shift in thinking from adult screening to childhood screening [21]. In view of the rapid development of genetic and molecular diagnostic technologies in recent years, the detection rate of FH in patients with dyslipidemia in China has also been increasing [5, 10]. Therefore, we call for early screening and early intervention for FH patients. Providing statins and other lipid-regulating drugs to FH patients in their early life will be of great significance for effectively preventing early CVD events.

Although gender differences may also lead to different lipid levels in FH patients [22, 23], the current study showed that serum TC value still presents an obvious positive correlation with age after adjusting for gender, and age accumulation will be the increase in blood lipid TC, whether the patients is male or female. Therefore, gender differences will not lead to an increase in lipid levels in FH patients or age-related changes. Additionally, smoking is considered to be a risk factor for cardiovascular diseases, and it is also believed to cause an increase in serum lipids such as TC, LDL-C and TG [24-26]. However, in our study, compared with the male non-smoking group, the serum TC concentration in the male smoking group decreased with age. Although this trend was not statistically significant (possibly limited by sample size), it still suggested that we cannot ignore the possibility of reduced TC values due to smoking, since smoking has been reported to be associated with lower cholesterol, which reduce the risk of death from CVD [27]. In addition to smoking, some factors that affect the progression of atherosclerosis, such as alcohol consumption, Lp(a), glucose metabolism, blood pressure, and the use of lipid-regulating drugs, also affect lipid metabolism and lead to changes in the TC level. Nevertheless, after adjusting for these influencing factors in this study, the results also showed an independent association between age and [cholesterol](#) level in the FH group. They also suggested that age was an independent risk factor for serum [cholesterol](#) level change in the FH group. Moreover, this was not seen in the control group. The results of this study showed that serum TC in the FH group was also significantly positively correlated with SBP, but not in the control group. This suggested a mutual interaction between cholesterol and arterial blood pressure in the FH group that was independent of the normal population. In support of this, it was found that elevated serum cholesterol levels led to decreased arterial wall compliance, resulting in increased cardiac after-load and increased SBP due to the accelerated return of systolic arterial waves from the periphery, which further led to left ventricular over-pressure [28, 29]. Additionally, the positive correlation between age and SBP under the action of this

mechanism further expands the age exposure effect of cholesterol-induced atherosclerosis, which could explain, to some extent, why FH patients have a risk of CVD events that is tens of times higher than that of the general population [30]. It is worth mentioning in this study that population characteristics showed that FH men accounted for only 39%, which does not match the current situation: that the proportion of men in the Chinese population is much higher than that of women. Indeed, as an autosomal genetic disease, FH has a 50/50 ratio of men to women in the population. Thus, we have to consider the possibility of early death in men with FH [31, 32], which further underlines the need for the cascade screening of family members with known indicator cases.

With the progression of urbanization, family members are often distributed in different places with different environments and have differences in their way of life and diet, which may mask some clinical characteristics of FH. For example, xanthoma and lipid profile changes are not obvious [5, 33], which increases the difficulty of collecting detailed information regarding FH. The collaboration of clinical, public health, and advocacy groups should therefore be encouraged to promote genetic screening for FH [34]. Our current research, through the strict screening of raw data, was based on a relatively small number of samples. Therefore, further large cohort studies are necessary to clarify the correlation between age and serum TC among subgroups of patients with FH. In addition, because FH has no independent code in the World Health Organization's international classification of diseases, it is difficult to estimate the number of people diagnosed with this disease or the proportion of people with FH in the general population. In the current situation, where there still exists a deficiency in the diagnosis and treatment of FH, there is an urgent need to implement screening and early treatment for this extremely high-risk disease [31].

Our study has some limitations. First, genetic diagnosis was not performed in FH patients who were diagnosed according to the DLCN criteria. Second, although our actual sample size exceeds the theoretical sample size obtained according to the calculation formula, it is still necessary to further verify the investigation with a larger sample size. Third, we excluded participants younger than 18 years old, which might lead to selection bias and limit the extrapolation of our results.

5. Conclusions

Age is an independent factor influencing the serum TC level in FH families; thus, it is necessary to conduct early screening and early intervention based on dyslipidemia, especially in children and adolescents, to reduce the premature occurrence of CVD events in FH patients.

Declarations

Ethics statement:

The study was conducted according to the guidelines of the Declaration of Helsinki, and retrospectively approved by the Ethics Committee of The First Hospital of Lanzhou

University (protocol code: LDYYLL2021-364, and date of approval: December 2, 2021).

Consent for publication:

This is a retrospective study, thus, it is not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' Contributions:

Conceptualization, Yanpei Zhang and Zhijie He; Data curation, Jinchun He; Formal analysis, Yaodong Wang; Funding acquisition, Jinchun He; Investigation, Yaodong Wang and Jinchun He; Methodology, Yaodong Wang; Project administration, Jinchun He; Resources, Jinchun He; Software, Yaodong Wang; Supervision, Jinchun He; Validation, Yaodong Wang, Yanpei Zhang, Zhijie He and Jinchun He; Visualization, Yaodong Wang and Yanpei Zhang; Writing – original draft, Yaodong Wang; Writing – review & editing, Yaodong Wang and Zhijie He.

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References

1. Austin, M.A., et al., *Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review*. Am J Epidemiol, 2004. **160**(5): p. 407-20.
2. Brautbar, A., et al., *Genetics of familial hypercholesterolemia*. Curr Atheroscler Rep, 2015. **17**(4): p. 491.
3. Hu, P., et al., *Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis*. Circulation, 2020. **141**(22): p. 1742-1759.
4. Kitahara, H., et al., *Prevalence of Achilles tendon xanthoma and familial hypercholesterolemia in patients with coronary artery disease undergoing percutaneous coronary intervention*. Heart Vessels, 2019. **34**(10): p. 1595-1599.
5. Tomlinson, B., M. Hu, and E. Chow, *Current status of familial hypercholesterolemia in Chinese populations*. Curr Opin Lipidol, 2019. **30**(2): p. 94-100.
6. Alonso, R., et al., *Early diagnosis and treatment of familial hypercholesterolemia: improving patient outcomes*. Expert Rev Cardiovasc Ther, 2013. **11**(3): p. 327-42.
7. Daniels, S.R., *How to identify children with familial hypercholesterolemia*. J Pediatr, 2017. **183**: p. 2.
8. Plana, N., et al., *Lipid and lipoprotein parameters for detection of familial hypercholesterolemia in childhood. The DECOPIN Project*. Clin Investig Arterioscler, 2018. **30**(4): p. 170-178.
9. van El, C.G., et al., *Stakeholder Views on Active Cascade Screening for Familial Hypercholesterolemia*. Healthcare (Basel), 2018. **6**(3).
10. Besseling, J., et al., *Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers*. Atherosclerosis, 2014. **233**(1): p. 219-23.
11. D'Agostino, R.B., Sr., et al., *General cardiovascular risk profile for use in primary care: the Framingham Heart Study*. Circulation, 2008. **117**(6): p. 743-53.
12. Paquette, M., R. Dufour, and A. Baass, *The Montreal-FH-SCORE: A new score to predict cardiovascular events in familial hypercholesterolemia*. J Clin Lipidol, 2017. **11**(1): p. 80-86.
13. Pérez de Isla, L., et al., *Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study)*. Circulation, 2017. **135**(22): p. 2133-2144.
14. Schienkiewitz, A., et al., *Age, maturation and serum lipid parameters: findings from the German Health Survey for Children and Adolescents*. BMC Public Health, 2019. **19**(1): p. 1627.
15. Watts, G.F., et al., *Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation*. Int J Cardiol, 2014. **171**(3): p. 309-25.

16. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.* Circulation, 2002. **106**(25): p. 3143-421.
17. Ference, B.A., et al., *Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel.* Eur Heart J, 2017. **38**(32): p. 2459-2472.
18. Domanski, M.J., et al., *Time Course of LDL Cholesterol Exposure and Cardiovascular Disease Event Risk.* J Am Coll Cardiol, 2020. **76**(13): p. 1507-1516.
19. Fröbuis, A.C., D.Q. Matus, and E.C. Seaver, *Genomic organization and expression demonstrate spatial and temporal Hox gene colinearity in the lophotrochozoan Capitella sp. I.* PLoS One, 2008. **3**(12): p. e4004.
20. Krumlauf, R., *Hox genes in vertebrate development.* Cell, 1994. **78**(2): p. 191-201.
21. Henneman, L., et al., *Screening for Familial Hypercholesterolemia in Children: What Can We Learn From Adult Screening Programs?* Healthcare (Basel), 2015. **3**(4): p. 1018-30.
22. Pellegrini, M., et al., *Role of the sex hormone estrogen in the prevention of lipid disorder.* Curr Med Chem, 2014. **21**(24): p. 2734-42.
23. Tharu, B.P. and C.P. Tsokos, *A Statistical Study of Serum Cholesterol Level by Gender and Race.* J Res Health Sci, 2017. **17**(3): p. e00386.
24. Chelland Campbell, S., R.J. Moffatt, and B.A. Stamford, *Smoking and smoking cessation – the relationship between cardiovascular disease and lipoprotein metabolism: a review.* Atherosclerosis, 2008. **201**(2): p. 225-35.
25. Herath, P., et al., *Effect of cigarette smoking on smoking biomarkers, blood pressure and blood lipid levels among Sri Lankan male smokers.* Postgrad Med J, 2021.
26. Zong, C., et al., *Cigarette smoke exposure impairs reverse cholesterol transport which can be minimized by treatment of hydrogen-saturated saline.* Lipids Health Dis, 2015. **14**: p. 159.
27. Parsa, N., et al., *The Mutual Impact of Smoking and Low Cholesterol on All-Cause, Non-Cardiovascular, and Cardiovascular Mortalities in Males.* Am J Mens Health, 2018. **12**(6): p. 2128-2135.
28. Podolecka, E., W. Grzeszczak, and E. Żukowska-Szzechowska, *Correlation between serum low-density lipoprotein cholesterol concentration and arterial wall stiffness.* Kardiol Pol, 2018. **76**(12): p. 1712-1716.
29. Salvi, P., et al., *Arterial stiffening, pulse pressure, and left ventricular diastolic dysfunction.* Eur J Heart Fail, 2016. **18**(11): p. 1362-1364.
30. Béliard, S., et al., *High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry.* Atherosclerosis, 2018. **277**: p. 334-340.

31. Nordestgaard, B.G., et al., *Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society*. Eur Heart J, 2013. **34**(45): p. 3478-90a.
32. Neil, H.A., et al., *Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study*. Bmj, 2000. **321**(7254): p. 148.
33. Zhou, M. and D. Zhao, *Familial Hypercholesterolemia in Asian Populations*. J Atheroscler Thromb, 2016. **23**(5): p. 539-49.
34. Modell, S.M., et al., *Expert and Advocacy Group Consensus Findings on the Horizon of Public Health Genetic Testing*. Healthcare (Basel), 2016. **4**(1).

Figures

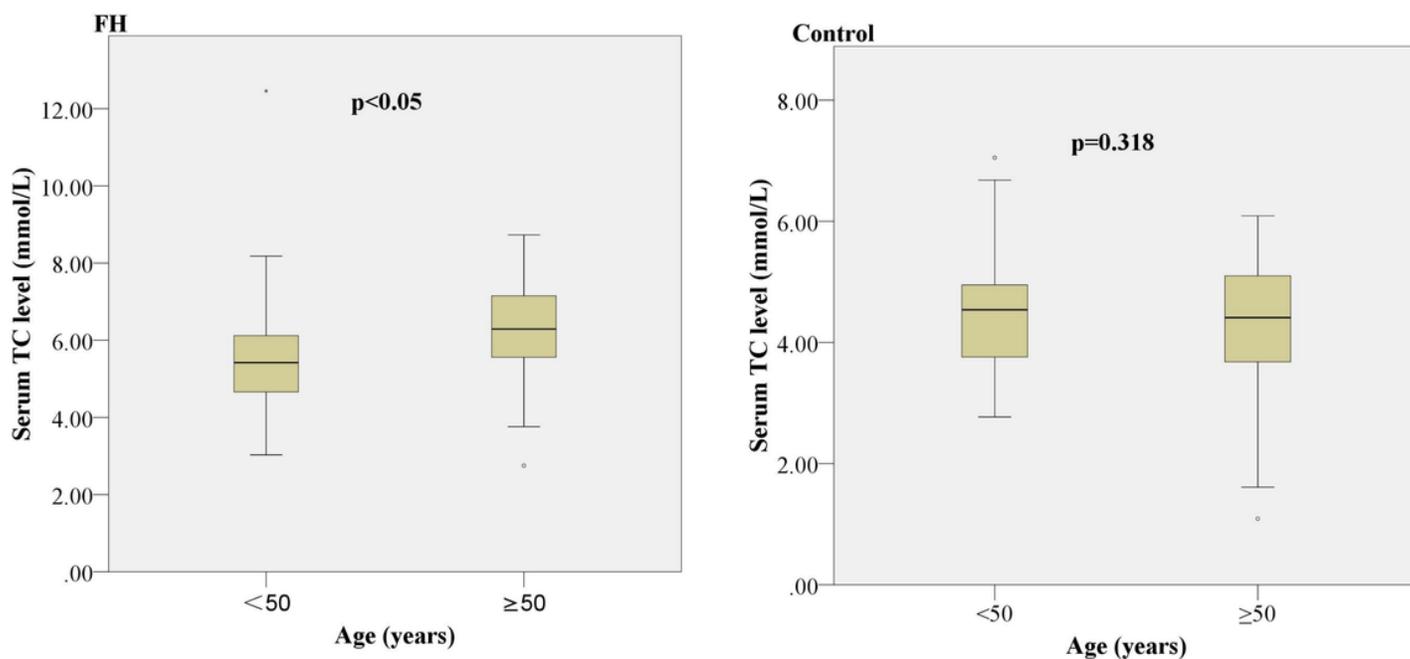


Figure 1

Comparison of serum TC level according to age in patients with FH (A) and control (B). TC, total cholesterol; FH, familial hypercholesterolemia.

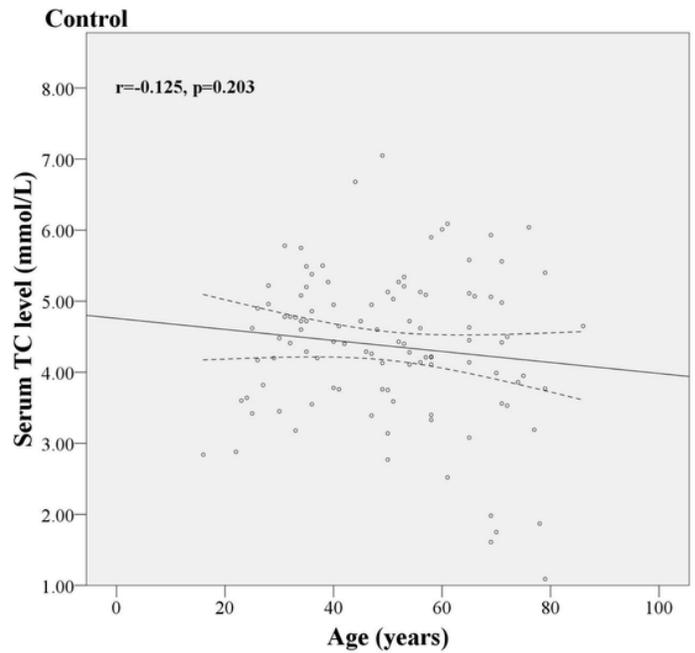
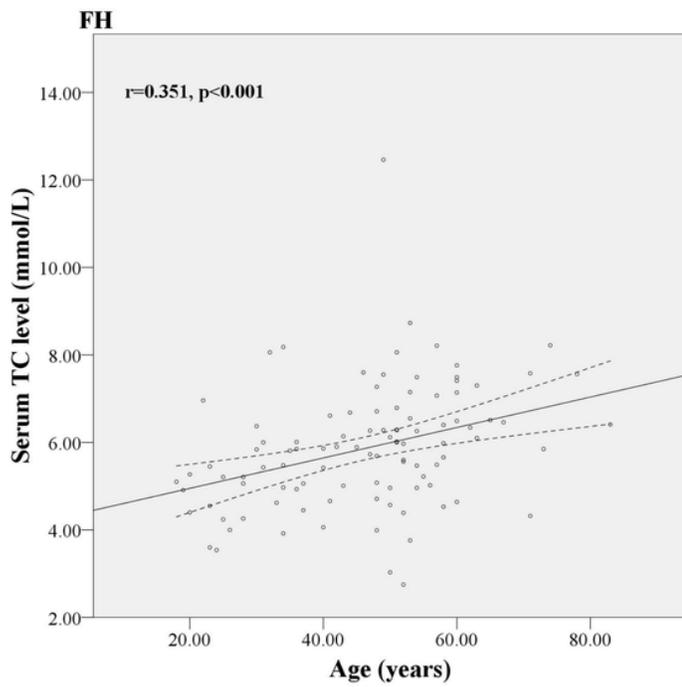


Figure 2

Correlations between age and serum TC levels in patients with FH (A) and control (B). Spearman correlation analyses were applied. The dotted lines indicate the 95% confidence intervals for the regression lines. TC, total cholesterol; FH, familial hypercholesterolemia.