Association between cholesterol and cardiac parameters.

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Abstract

It is well-known that atherosclerosis is a primary form of cardiovascular disease, in which cholesterol plaques form in the artery walls, and consequently restrict blood flow. This leads to less oxygen for the heart muscle, yielding cardiac problems. The current report examines the associations of total cholesterol and its components with the cardiac parameters. In addition, the effects of the total cholesterol and its components on cardiac parameters are focused in the present report.

Introduction

There is no specific cardiovascular disease (CVD) marker. Generally, total cholesterol (TC) is used as a cardiac disease marker as it is a principal cause of atherosclerosis and heart disease [1-4]. Several studies have shown the association between TC and CVD [5-10]. Recently, the Prospective Studies Collaboration (using meta-analysis) has shown the association between CVD and TC in all ages and in both sexes [11]. Though the association between TC and CVD mortality is observed in all ages and in both sexes [11], but the risk decreases as the age increases, and it is minimal more than age of 80 years [12]. However, there are several contradictions to the association between TC and CVD. Specifically, most of the Japanese epidemiological studies have focused that the high TC is not a risk factor for stroke [13-16].

It is well-known that TC is the sum of low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and very low-density lipoprotein (VLDL-C). Triglyceride is not included in TC. TC below 200 (mg/dL) is treated as normal, and more or equal to 200 (mg/dL) is recognized as high. The Centers for Disease Control and Prevention has analyzed data from 2005-2008, and it has examined incidence, prevalence, treatment, and control of high LDL-C levels [17]. It is observed that approximately 71 million American adults (33.5%) had high LDL-C levels, but only 34 million (48.1%) got treatment, and 23 million (33.2%) had their LDL-C controlled [17]. It is known that TC and CVD are associated in all ages in both the sexes [12], but a high LDL-C level is associated with a higher risk of CVD, while a high level of HDL-C is associated with a lower risk of CVD [18]. The medical practitioners first measure the total cholesterol levels to assess a patient's cardiac risk. For more specific guidance, the doctors divide the TC level by the HDL-C level. The CVD risk is minimized by having a lower TC level, and a higher proportion of HDL-C level. The ratio of TC to HDL-C should be less than 4 to 1.

It is mentioned as in the above that there may or may not be association between the cholesterol and its components with the cardiac parameters. The present report considers the following hypotheses. Is there any association between the cholesterol and its components with the cardiac parameters? What are the effects of cholesterol and its components on the cardiac parameters? These issues are examined in the current report based on real data analysis.

Background

Most of the earlier research articles have used the statistical techniques such as meta-analysis, simple product moment correlation coefficient, Logistic regression, classical simple & multiple regression analyses, Chi-square test [3,5,7,9,11,17] which are not appropriate for the analysis of positive, heteroscedastic, correlated, non-normally distributed data [19-21]. The physiological continuous random variables such as total cholesterol, low-density lipoprotein, high-density lipoprotein, ratio of TC to HDL-C, blood pressures (basal, systolic, diastolic, maximum), heart rates (basal, peak, maximum), cardiac ejection fractions are mostly heterogeneous, positive, and non-normally distributed [22-24]. Recently, a few articles [6,9,11,22,24] have considered the responses as positive, heteroscedastic and non-normally distributed, but the associations of TC, LDL-C, HDL-C and the ratio of TC to HDL-C with the cardiac parameters have not clearly focused. Based on the recent articles [6,22,24,25], and along with some new analyses, the present report focuses the associations of TC, LDL-C, HDL-C and the ratio of TC to HDL-C with the cardiac parameters. Most of the earlier research articles have assumed the distribution of the random variables (cholesterol and its components) as Normal. Practically, these random variables are non-Normally distributed [6,24]. Earlier used statistical techniques are mostly based on Normal distribution. The present data sets are positive, and their variances are non-constant, distributions are non-Normal, and the earlier used statistical methods are inappropriate. These issues have motivated us to examine the association between the cholesterol and its components with the cardiac parameters.

Methodology

The responses TC, LDL-C, HDL-C, the ratio of TC to HDL-C and cardiac parameters are positive, heterogeneous and non-normally distributed. These responses are generally modeled either by the gamma or the Log-normal joint generalized linear models (JGLMs) [20,22]. These two models and the analysis techniques are well described in [20-22]. Using link functions,

two models one for the mean and the other for the variance are derived using iteration process. For ready reference, these two models are shortly reproduced herein. For analyzing the positive response y_i's, Nelder and Lee [26] have derived a modeling technique, known as the joint generalized linear models (JGLMs) which is as follows.

For the positive response Y_i, generally, the log transformation $Z_i = \log Y_i$ is used. Assuming the log-normal distribution of Z_i a joint modeling of the mean and variance is such that

$E(Z_i) = \mu_{zi}$ and $Var(Z_i) = \sigma_{zi}^2$,

$\mu_{zi} = x_i^t \beta$ and $\log(\sigma_{zi}^2) = g_i^t \gamma$,

where x_i^t and g_i^t are the row vectors for the regression coefficients β and γ in the mean and dispersion model, respectively.

For a positive response y_i, if

$E(y_i) = \mu_i$ and $Var(y_i) = \sigma_i^2 V(\mu_i)$,

where $V(\cdot)$ is the variance function and σ_i^2's are the dispersion parameters, and $V(\mu) = \mu^2$, then the joint gamma models for the mean and the variance parameters are

$\varepsilon_i = h(\sigma_i^2) = w_i^t \gamma$ and $\varepsilon_i = h(\sigma_i^2) = w_i^t \gamma$,

where $g(\cdot)$ and x_i^t are GLM link functions for the mean and the variance, respectively; and x_i^t, w_i^t are respectively, the row vectors associated with the mean parameter β and the variance parameter γ. Maximum likelihood (ML) method is used for estimating the mean parameters β, while the restricted ML (REML) is used for estimating the dispersion parameter γ [20].

Materials

The present report has considered two secondary data sets which are given respectively [6,24]. The data descriptions, collection methods, patients population are clearly described in the related papers. For ready reference, the factors/ covariates are described herein.

First data set

The data set contains 366 subjects along with 20 factors/ covariates with all non-missing information (Table 1) [6]. It can be downloaded at http://biostat.mc.vanderbilt.edu/ wiki/ Main/DataSets?CGISESSID=10713f6d891653ddcbb7ddbdd9cf fb79. The factors/ variables of the data set are age, sex (male=1, female=2), total cholesterol (TC), high density lipoprotein (HDL-C), lipid ratio= cholesterol/HDL-C (Ratio), glycosolated hemoglobin (GLYHB), stabilized glucose (STB.GL), subject's height (Height), subject's weight (Weight), body mass index (BMI), frame (1=small, 2=medium, 3=large) (Frame), location (1=Buckingham, 2=Louisa) (Location), first diastolic blood pressure (BP.1d), first systolic blood pressure (BP.1s), second diastolic blood pressure (BP.2d), second systolic blood pressure (BP.2s), subject's hip measurement (Hip), subject's waist measurement (Waist), index of fat distribution (=waist/hips ratio) (IFD), postprandial time when labs were drawn (TIM.PN).

The data set contains total cholesterol (TC), high density lipoprotein (HDL-C), lipid ratio=cholesterol/HDL-C (Ratio), and cardiac parameters such as first diastolic blood pressure (BP.1d), and first systolic blood pressure (BP.1s). Only the analysis of TC is given in [6]. The analyses of HDL-C, lipid

ratio, BP.1d, and BP.1s have been derived based on both the log-normal and gamma models. Based on the current analyses and TC analysis from [6], the following associations between TC and its components with the cardiac parameters are reported as follows.

* From [6], TC analysis shows the following associations. The mean TC is separately negatively *insignificantly* associated with HDL-C (P=0.920) and the lipid ratio (P=0.318), while it is positively *significantly* associated with the joint interaction effect of HDL-C and lipid ratio (P<0.001). The variance of TC is negatively *insignificantly* associated with the first systolic blood pressure (BP.1s) (P=0.968), while it is negatively *significantly* associated with the first diastolic blood pressure (BP.1d) (P<0.001), indicating that the patients with higher BP.1d have lower TC variance. But the joint interaction effect of BP.1s & BP.1d (P=0.084) is positively significantly associated with the TC variance.

*The high density lipoprotein (HDL-C) analysis shows the following associations. The mean HDL-C is positively *significantly* associated with the TC (P<0.001), and it is inversely *significantly* associated with the lipid ratio (P<0.001). The mean HDL-C is negatively *insignificantly* associated with the first systolic blood pressure (BP.1s) (P=0.188), while it is positively *significantly* associated with the first diastolic blood pressure (BP.1d) (P=0.039). The variance of HDL-C is positively *significantly* associated with the first diastolic blood pressure (BP.1d) (P=0.058).

*The lipid ratio (TC/HDL-C) analysis shows the following associations. The mean lipid ratio is positively *significantly* associated with the TC (P<0.001), and it is inversely *significantly* associated with the HDL-C (P<0.001). The variance of the lipid ratio is negatively *significantly* associated with the first diastolic blood pressure (BP.1d) (P=0.002).

*The first diastolic blood pressure (BP.1d) analysis shows the following associations. The mean first diastolic blood pressure (BP.1d) is positively *insignificantly* associated with the TC (P=0.198). It is positively *significantly* associated with the HDL-C (P=0.031) and the first systolic blood pressure (BP.1s) (P<0.001). The variance of BP.1d is positively *insignificantly* associated with the BP.1s (P=0.192).

*The first systolic blood pressure (BP.1s) analysis shows the following associations. The mean BP.1s is positively *insignificantly* associated with the TC (P=0.348), and it is positively *significantly* associated with the BP.1d (P<0.001). All the above summarized results are given in Table 1.

Second data set

The data set is taken from Modeling of Biochemical Parameters [24]. It contains 64 subjects with 21 factors/ variables which are age, sex, weight, height, body mass index, obesity, lifestyle, dietary habits like eating in outside (no=0, yes=1), smoking habit (no=0, yes=1), types of oil consumption, family blood pressure (no=0, yes=1) (BP), family history (FH) of diabetes mellitus (no=0, yes=1) (DM), hypertension with coronary heart disease (no=0, yes=1) (CHD), history of any drug intake (no=0, yes=1), history of past illness (no=0, yes=1), fasting plasma glucose level (PGL), serum triglyceride (STG), total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), fasting serum insulin (FI).

Table 1. *Associations of TC, HDL-C, lipid ration with cardiac parameters (1st data set).*

Response	Associated with	Estimate	Standard error	t-value	P-value	Association type
Mean TC	HDL-C	-0.001	0.001	-0.401	0.689	Insignificant
	Lipid ratio	-0.004	0.001	-1.39	0.165	Insignificant
	HDL-C*ratio	0.005	0.001	64.34	<0.001	Positive
Variance of TC	BP.1s	-0.001	0.021	-0.04	0.968	Insignificant
	BP.1d	-0.112	0.031	-3.76	<0.001	Negative
	BP.1s*BP.1d	0.001	0.001	1.73	0.084	Positive
Mean HDL-C	TC	0.005	0.001	51.26	<0.001	Positive
	Lipid ratio	-0.219	0.003	-76.43	<0.001	Negative
	BP.1s	0.001	0.001	-1.39	0.188	Insignificant
	BP.1d	0.001	0.001	2.00	0.039	Positive
Variance of HDL-C	BP.1d	0.008	0.006	1.903	0.058	Positive
Mean Lipid ratio	TC	0.005	0.001	55.48	<0.001	Positive
	HDL-C	-0.018	0.001	-81.90	<0.001	Negative
Variance of ratio	BP.1d	-0.018	0.006	-3.07	0.002	Negative
Mean BP.1d	TC	0.001	0.001	1.29	0.198	Insignificant
	HDL-C	0.001	0.001	2.17	0.031	Positive
	BP.1s	0.005	0.001	15.28	<0.001	Positive
Variance of BP.1d	BP.1s	0.004	0.003	1.31	0.192	Insignificant
Mean BP.1s	TC	0.001	0.001	0.94	0.348	Insignificant
	BP.1.d	0.001	0.001	16.12	<0.001	Positive

Associations

The above data set contains TC, LDL-C, HDL-C, and two cardiac parameters family blood pressure (no=0, yes=1) (BP), hypertension with coronary heart disease (no=0, yes=1) (CHD). The analyses of TC, LDL-C and HDL-C are given in [24]. Family blood pressure and hypertension with coronary heart disease are both categorical characters. The analyses of these two cardiac parameters are not given in Modeling of Biochemical Parameters [24]. Based on the analyses of TC, HDL-C and LDL-C [24], the associations of TC and its components with the two cardiac parameters are presented herein.

*Analysis of total cholesterol (TC) (Table 2) [24] shows that mean TC (or variance of TC) is positively associated with HDL-C (P=0.001). Analysis of LDL-C [24] shows that mean LDL-C is positively associated with TC (P<0.001), while it is negatively associated with the HDL-C (P<0.001). The mean LDL-C is positively associated the coronary heart disease (CHD) (P<0.001), while it is negatively associated with the family blood pressure (BP) (P<0.001). HDL-C analysis does not show any significant association with any cardiac parameter for this data set. All the summarized results for this data set is given in Table 2.

Concluding Remarks

The current report focuses the associations between total cholesterol and its components with some cardiac parameters. Here we have considered TC, HDL-C, LDL-C, lipid ratio (TC/HDL-C). We have not considered very low-density lipoprotein (VLDL-C), as we have no information for VLDL-C in any set of considered data. There are many cardiac parameters such as basal, systolic, diastolic, maximum blood pressures, basal, peak, maximum heart rates and cardiac ejection fractions. Here we have only systolic, diastolic blood pressure, family blood pressure and hypertension with coronary heart disease (CHD). The present report has shown some associations between TC and its components with the systolic, diastolic, family blood pressures and CVD. In addition, it has shown the associations between TC and its components along with the lipid ratio. Moreover, it has shown the associations between the systolic and diastolic blood pressures. Serum triglyceride (STG) is not included in TC, but TC is positively associated with STG (P<0.001) (Table 2) [24]. Moreover, STG is negatively associated with the HDL-C (P=0.024) and family blood pressure (P=0.041). These two results are included in Table 2.

For the first data set, joint interaction effect of HDL-C and lipid ratio (HDL-C*ratio) is positively significantly associated with the mean TC. Note that HDL-C and lipid ratio (both insignificant

Table 2. *Associations of TC, HDL-C, LDL-C with cardiac parameters (for 2nd set data).*

Response	Associated with	Estimate	Standard error	t-value	P-value	Association type
Mean TC	HDL-C	0.008	0.001	3.056	0.001	Positive
	Serum triglyceride(STG)	0.002	0.001	8.80	<0.001	Positive
Variance of TC	HDL-C	0.042	0.021	2.96	0.001	Positive
Mean LDL-C	TC	0.012	0.001	19.46	<0.001	Positive
	HDL-C	-0.023	0.001	-11.07	<0.001	Negative
	coronary heart disease (CHD)	0.011	0.031	3.26	0.001	Positive
	family blood pressure (BP)	-0.141	0.031	-4.72	<0.001	Negative
	STG	-0.003	0.001	-10.59	<0.001	Negative
Mean STG	TC	0.012	0.001	5.46	<0.001	Positive
Mean STG	HDL-C	-0.011	0.011	-2.14	0.024	Negative

effects) are included in the model due to marginality rule by Nelder [27]. Nelder's marginality rule states that if any higher order interaction effect is significant, then all its lower order effects should be included in the model. It is known that HDL-C is a part of TC, and the lipid ratio is a direct function of TC, so their joint interaction effect should be positively associated with TC. Variance of TC is positively associated with the joint interaction effect of BP.1s and BP.1d (BP.1s*BP.1d). Mean and variance of HDL-C is also separately positively associated with the BP.1d. Variance of lipid ratio is negatively associated with the BP.1d. For the second data set, mean LDL-C is positively associated with coronary heart disease (CHD), and it is negatively associated with the family blood pressure. These results show that TC and its components are associated with cardiac parameters and events.

The considered two data sets are not very good to examine the association between TC and its components with the cardiac parameters, as the first data set is for the diabetic patients, and the second data set is for the young Indian medical students under age 24 years. An ideal data for this study should be the cardiac patients with STG, TC, all the components of TC, and along with all possible cardiac parameters and events. The present report has shown some associations between TC and its components with the cardiac parameters. The first data set contains TC and HDL-C but no LDL-C, whereas the second data set contains all the three. For the second data set, LDL-C has shown many associations with the cardiac parameters than TC, but HDL-C has shown no association (Table 2). It has established that TC and its components have some effects on cardiac parameters. Medical practitioners and every individual should care on total cholesterol and its components.

Conflict of Interest: The author confirms that this article content has no conflict of interest

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