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Research Paper

Longitudinal Associations between Triglycerides and Metabolic Syndrome Components in a Beijing Adult Population, 2007-2012

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Abstract

Background: Longitudinal associations between triglycerides (TG) and other metabolic syndrome (MetS) components have rarely been reported. The purpose was to investigate the longitudinal association between TG and other MetS components with time.

Methods: The longitudinal study was established in 2007 on individuals who attended health check-ups at Beijing Tongren Hospital and Beijing Xiaotangshan Hospital. Data used in this study was based on 7489 participants who had at least three health check-ups over a period of 5-year follow up. Joint model was used to explore longitudinal associations between TG and other MetS components after adjusted for age.

Results: There were positive correlations between TG and other MetS components except for high density lipoprotein (HDL), and the correlations increased with time. A negative correlation was displayed between TG and HDL, and the correlation also increased with time. Among all five pairs of TG and other MetS components, the marginal correlation between TG and body mass index (BMI) was the largest for both men and women. The marginal correlation between TG and fasting plasma glucose was the smallest for men, while the marginal correlation between TG and diastolic blood pressure was the smallest for women.

Conclusions: The longitudinal association between TG and other MetS components increased with time. Among five pairs of TG and other MetS components, the longitudinal correlation between TG and BMI was the largest. It is important to closely monitor subjects with high levels of TG and BMI in health check-up population especially for women, because these two components are closely associated with development of hypertension, diabetes, cardiovascular disease and other metabolic diseases.

Key words: Triglycerides, Metabolic syndrome components, Longitudinal correlation, Joint model

Introduction

Metabolic syndrome (MetS) refers to a group of inter-related risk factors that include hyperglycemia, elevated blood pressure (BP), elevated triglycerides (TG), low high-density lipoprotein (HDL) levels, and obesity (in particular, central obesity) [1]. MetS is a strong predictor of cardiovascular disease (CVD), diabetes, stroke, and all-cause mortality, and is becoming a major public-health challenge worldwide [2-6]. Although, it is not yet clear whether MetS has a single cause, it is acknowledged that the most critical pathophysiology is insulin resistance [7, 8], and therefore the importance of central obesity was

established [9].

Hypertriglyceridemia is often observed in subjects with MetS, type 2 diabetes, stroke, or combined with hyperlipidemia [10, 11]. The level of TG is an independent risk factor for CVD events, independent of serum HDL or low-density lipoprotein (LDL) levels [12]. A number of meta-analyses have been published demonstrating associations between TG levels and CVD risk, independent of HDL level [13, 14].

There are several cross-sectional studies regarding the association between TG and other MetS components. In a cross sectional survey study on 266 Turkish elderly aged people, TG was reported to be significantly correlated with weight, body mass index (BMI), waist circumference (WC), waist/hip and waist/height [15]. In another study involving healthy Japanese women, high level of TG was also associated with increased level of BMI [16]. Other two studies have also recognized positive correlation between TG and other metabolic risk factors using partial correlation analysis and pearson correlation analysis [17, 18]. However, there have been limited data about longitudinal associations between TG and other MetS components. To fully understand the longitudinal association between TG and other MetS components, longitudinal studies are required, especially using repeated measures of MetS components.

Therefore, the aim of the present study was to assess longitudinal associations between TG and other MetS components in a Beijing adult population from 2007 to 2012.

Methods

Participants

The longitudinal study was set up in 2007 on adults who attended health check-ups at Beijing Tongren Hospital and Beijing Xiaotangshan Hospital. A total of 7489 subjects with at least three health check-ups in the 5-year follow-up were enrolled in the study. Individuals with a previous diagnosis of CVD, cerebral infarction, gastric cancer, or those who had undergone coronary artery bypass surgery, coronary stenting surgery or gastrectomy, or those who had MetS, obesity, dyslipidemia, hyperglycemia, or hypertension at baseline were excluded. The study was approved by the ethics committee of Capital Medical University of China, and performed in accordance with the principles of Declaration of Helsinki (2013SY26). All participants gave their informed written consents.

Definition of MetS

MetS was diagnosed if participants had three or more of the following risk determinants according to the Joint Interim Statement criteria [1]. However, WC was not measured because of limited health check-up site, and BMI was taken as a substitute for the component of obesity [19]. The determinants were as follows:

- Obesity: BMI ≥ 28 kg/m^2;
- Elevated TG (drug treatment for elevated TG is an alternate indicator) ≥ 150 mg/dL (1.7 mmol/L);
- Reduced HDL (drug treatment for reduced HDL is an alternate indicator) < 40 mg/dL (1.0 mmol/L) in males, < 50 mg/dL (1.3 mmol/L) in females;
- Elevated BP (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator) systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg;
- Elevated fasting plasma glucose (FPG) (drug treatment of elevated glucose is an alternate indicator) ≥ 100 mg/dL.

Measurements

The participants underwent routine physical examinations that included the measurement of height, weight, BP, and overnight fasting blood sampling. Weight and height were measured without shoes, and BMI was calculated as weight (kg) divided by squared height (m). The measurement of weight was undergone at least twice for the improvement of reliability. The intra variability of weight was < 5%. BP was measured on the right upper arm and maintained at the level of the heart with participants in sitting position. BP was measured by trained and certified nurses working in Beijing Tongren Hospital and Beijing Xiaotangshan Hospital. Before measuring BP, subjects were at rest for at least 5 minutes. The trained nurse will measure BP three times in the following 30 minutes. During the 30 min preceding the measurements, the subjects were required to refrain from smoking or consuming caffeine. A standard mercury sphygmomanometer was used with 1 of 4 cuff sizes (pediatric, regular adult, large adult, or thigh) based on the participant's arm circumference. Three readings of SBP and DBP were recorded, and the average of the last two measurements was used for data analysis.

Blood samples were obtained from antecubital vein into tubes containing ethylenediaminetetraacetic acid (EDTA) in the morning after an overnight fasting period. Then the samples were stored in 4°C refrigerator, and they will be analyzed in 8 hours. HDL, TG, and FPG were measured by enzymatic method using a chemistry analyzer (Beckman LX 20, America) at Department of Clinical Laboratory in

Beijing Tongren Hospital and Beijing Xiaotangshan Hospital. All analyses performed in accordance with the manufacturer's recommendations.

Statistical Analysis

Missing Data Imputation and Data analysis

To account for missing values, multiple imputation (MI) was performed. Because the imputation method of choice depended on the pattern of missing data and the type of the imputed variables, the Markov Chain Monte Carlo method was chosen to avoid loss of generality. The MI procedure of SAS software package (version 9.2; SAS Institute, Chicago, IL, USA) was used [20].

Data were expressed as mean ± standard deviation or, for non-normally distributed variables, as median and interquartile range. To compare the differences between groups, student's *t* test or Wilcoxon rank sum test was used to determine differences between groups. Joint model was conducted using SAS mixed procedure to account for longitudinal correlations between TG and other MetS components. Data were analyzed using SAS software package and $P < 0.05$ was considered as significant.

When there were two continuous response variables, Y_1 and Y_2, they were measured over time for a number of subjects. Each of the variables was described using the linear mixed-effects model:

$$Y_{1i}(t)=\mu_1(t)+a_{1i}+b_{1i}t+\varepsilon_{1i}(t)$$

$$Y_{2i}(t)=\mu_2(t)+a_{2i}+b_{2i}t+\varepsilon_{2i}(t)$$

The marginal correlation between Y_1 and Y_2 at time t is given by:

$$r_M(t)=\frac{Cov(Y_{1i}(t),Y_{2i}(t))}{\sqrt{Var(Y_{1i}(t))\times Var(Y_{2i}(t))}}=\frac{\sigma_{a_1a_2}+t\sigma_{a_1b_2}+t\sigma_{a_2b_1}+t^2\sigma_{b_1b_2}}{\sqrt{(\sigma_{a_1}^2+2t\sigma_{a_1b_1}+t^2\sigma_{b_1}^2+\sigma_1^2)\times(\sigma_{a_2}^2+2t\sigma_{a_2b_2}+t^2\sigma_{b_2}^2+\sigma_2^2)}}$$

Table 1. Basic characteristics and MetS components of subjects in 2007 and 2012

Year	Variables	Men	Women	*t*	*P*
2007	*N*	3389	4100	–	–
	age	41.55±10.81	41.03±10.24	-2.13	0.0332
	BMI (kg/m²)	23.42±2.50	21.80±2.53	-27.88	<0.0001
	FPG (mmol/L)	4.88±0.42	4.86±0.40	-2.12	0.0341
	HDL (mmol/L)	1.35±0.27	1.63±0.30	43.27	<0.0001
	SBP (mmHg)	111.25±9.11	105.94±10.43	-23.49	<0.0001
	DBP (mmHg)	73.72±6.58	69.87±7.42	-23.76	<0.0001
	TG (mmol/L)	1.04±0.35	0.85±0.34	-24.62	<0.0001
2012	*N*	1744	2171	–	–
	BMI (kg/m²)	24.26±2.70	22.45±2.81	-20.36	<0.0001
	FPG (mmol/L)	5.16±0.53	5.05±0.45	-6.94	<0.0001
	HDL (mmol/L)	1.27±0.28	1.57±0.33	30.61	<0.0001
	SBP (mmHg)	119.58±13.32	113.24±14.33	-14.31	<0.0001
	DBP (mmHg)	73.03±9.80	69.56±9.71	-11.08	<0.0001
	TG (mmol/L)	1.33±0.74	1.04±0.53	-14.06	<0.0001

Abbreviations: MetS = metabolic syndrome; BMI = body mass index; FPG = fasting plasma glucose; HDL= high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides.
–: Test was not performed on sample size (*n*).

Table 2. Fixed-Effects Tests of age for all subjects

Pairs of MetS components	Outcome	Men		Women	
		t#	*p*#	*t*#	*p*#
TG and BMI	TG	7.73	<0.0001	20.79	<0.0001
	BMI	7.62	<0.0001	24.28	<0.0001
TG and FPG	TG	7.30	<0.0001	20.70	<0.0001
	FPG	6.40	<0.0001	3.93	<0.0001
TG and HDL	TG	8.46	<0.0001	22.17	<0.0001
	HDL	1.89	0.0582	-2.72	0.0066
TG and SBP	TG	7.43	<0.0001	17.07	<0.0001
	SBP	11.55	<0.0001	24.20	<0.0001
TG and DBP	DBP	13.80	<0.0001	21.46	<0.0001
	TG	7.23	<0.0001	20.73	<0.0001

Abbreviations: MetS = metabolic syndrome; BMI = body mass index; FPG = fasting plasma glucose; HDL= high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides.
#: Joint Model was used.

Results

Basic characteristics and MetS components of the subjects

The basic characteristics and MetS components of the study population in 2007 and 2012 were shown in Table 1. There were 7489 individuals included in the study in 2007 at baseline (3389 men, 41.55±10.81 years; 4100 women, 41.03±10.24 years). Significant differences were displayed in the levels of age, BMI, FPG, HDL, SBP, DBP, and TG between men and women.

Results of Joint Model

Fixed-effects tests for age are displayed in Table 2. It was indicated that age had significant effects on the development of TG, BMI, FPG, SBP and DBP for men. And age had significant effects on the development of all MetS components for women.

The marginal correlations between TG and other MetS components after adjusted for age are presented in Table 3, Figure 1 and Figure 2.

Longitudinal correlations between TG and other MetS components for men adjusted for age were presented in Figure 1. There were positive correlations between TG and other MetS components except for HDL, and the correlations gradually increased with time. A negative correlation was displayed between TG and HDL, and the correlation also increased with time. Among all five pairs of TG and other MetS components, the marginal correlation

between TG and BMI was the largest, and the marginal correlation between TG and FPG was the smallest.

Longitudinal correlations between TG and other MetS components for women adjusted for age were displayed in Figure 2. Positive associations were detected between TG and other MetS components except for HDL, and the correlations increased rapidly with time. TG was negatively correlated with HDL, and the correlation also increased with time. Among all the five cases, the marginal correlation between TG and BMI was the largest, and the marginal correlation between TG and DBP was the smallest.

Table 3. The marginal correlation between TG and other MetS components for all subjects

	Pairs of MetS components	2007	2008	2009	2010	2011	2012
Men	TG and BMI*	0.2423	0.2433	0.2571	0.2792	0.3060	0.3350
	TG and FPG*	0.0654	0.0649	0.0777	0.0980	0.1213	0.1450
	TG and HDL*	-0.1583	-0.1682	-0.1891	-0.2173	-0.2500	-0.2848
	TG and SBP*	0.0830	0.0973	0.1170	0.1391	0.1616	0.1832
	TG and DBP*	0.0959	0.1092	0.1282	0.1495	0.1710	0.1915
Women	TG and BMI*	0.2140	0.3919	0.4793	0.5235	0.5479	0.5624
	TG and FPG*	0.0696	0.1518	0.1967	0.2201	0.2331	0.2409
	TG and HDL*	-0.1708	-0.3429	-0.4312	-0.4765	-0.5016	-0.5166
	TG and SBP*	0.0927	0.2218	0.3000	0.3426	0.3668	0.3814
	TG and DBP*	0.0818	0.0909	0.1051	0.1227	0.1421	0.1621

Abbreviations: MetS = metabolic syndrome; BMI = body mass index; FPG = fasting plasma glucose; HDL= high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides.
*: $P<0.001$

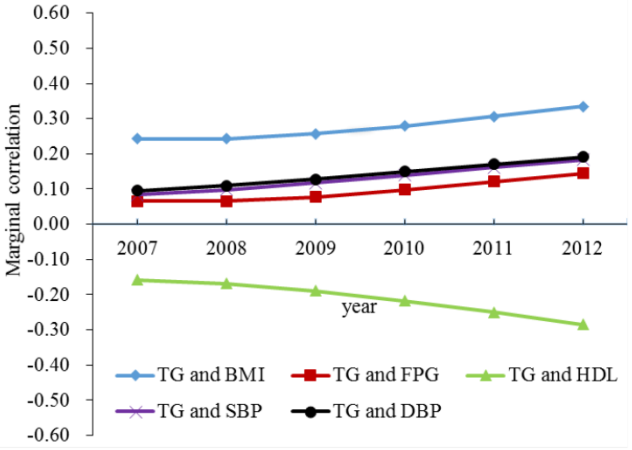


Figure 1. The marginal correlations between TG and other MetS components for men. Abbreviations: BMI = body mass index; FPG = fasting plasma glucose; HDL= high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; MetS = metabolic syndrome.

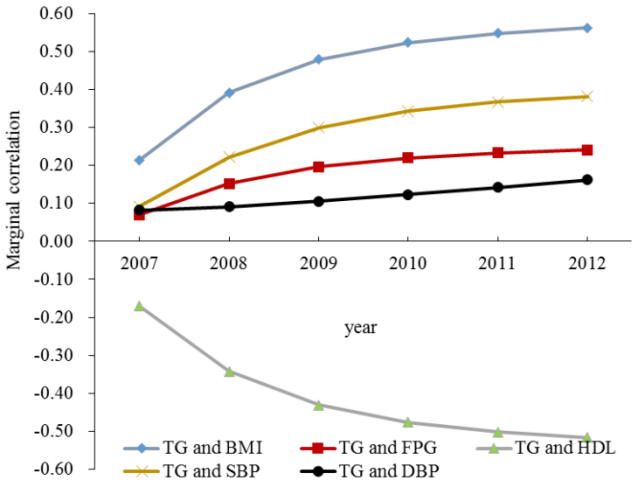


Figure 2. The marginal correlations between TG and other MetS components for women. Abbreviations: BMI = body mass index; FPG = fasting plasma glucose; HDL= high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; MetS = metabolic syndrome.

Discussion

Longitudinal associations between TG and other MetS components over time have rarely been considered in previous studies. Joint model is a novel method detecting longitudinal association between two outcomes.

Joint modeling two MetS components, rather than modeling them independently, and therefore incorporates additional information into the model that may increase estimation and prediction accuracy. Joint model has often been applied for longitudinal measurements and time-to-event data [21, 22]. The model also has been used for two longitudinal continuous measurements. One previous study using the joint model detected a very strong association between the development of two hearing thresholds and a slowly increasing change in the association between these thresholds over time [23]. However, there are few inferences about using the joint model to analyze the longitudinal association between TG and other MetS components with time.

In the present study, longitudinal associations between TG and other MetS components were assessed after adjusted for age. It was suggested that the marginal correlation between TG and BMI was the largest and the correlation increased with time for both men and women. And the correlation between TG and BMI is larger for women than men. The positive association was also reported in previous literature using partial correlation analysis in a cross sectional study [17]. But no inference has shown the longitudinal association between TG and BMI. Positive association between TG and BMI was also

detected in the present study, as shown previously [19, 24]. Therefore, it is important to closely monitor subjects with high levels of TG and BMI especially for women, because these two components are closely associated with development of hypertension, diabetes, CVD and other chronic diseases.

The marginal correlation between TG and FPG was positive and increased with time for men and women. But the correlation between TG and FPG is larger for women than men. Previous literatures have suggested that individuals with elevated FPG usually have a number of other metabolic abnormalities, including elevated TG, and elevated BP [24-26]. It has been reported that lipotoxicity by deposition of TG may be associated with beta-cell dysfunction and insulin resistance [27].

The marginal correlation between TG and HDL increased with time for both genders. The correlation between TG and HDL was extremely larger for men than women. The strong association between TG and HDL were consistent with previous results [25, 28, 29]. One study has shown that an increase in TG level is commonly associated with a reduction in HDL level [30]. It has been indicated that hypertriglyceridemia stimulates the enzymatic activity of cholesterol ester transfer protein, which facilitates the transfer of TG from TG-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters [31]. This leads to an increase in TG content of HDL and LDL.

The marginal correlation between TG and BP increased slowly with time for men and women in the present study. The correlation between TG and SBP was a little larger for women than men. But the correlation between TG and DBP for men was slightly larger for men than women. One previous study has shown a significant increase in plasma TG level as BP levels increased from optimally normal, across high-normal to hypertensive levels [32].

The strength of this research was that it was a longitudinal study of 5 years in a Beijing adult population. The present study assessed longitudinal association between TG and other MetS components for the first time. The limitation was the lack of WC as an indicator for central obesity, however, BMI was used for substitute. One study showed that the two measures of BMI and WC are closely correlated [33]. Another study indicated that most individuals with an abnormal BMI also have an abnormal WC. Both indexes of excess adiposity are positively associated with SBP, FPG, and TG and inversely associated with HDL [34]. One study based on a cross-sectional field survey targeted adults in China demonstrated that dyslipidemia, particularly hypertriglyceridemia and low HDL is associated with central obesity (measured with WC) using multivariate logistic regression [35]. A previous study used both BMI and WC has shown that either of the two measures can be recommended in screening for MetS in routine clinical practice in order to combat CVD and type 2 diabetes [36]. In addition, this study was based on an adult population of health check-up. This limits the generalizability of the data to other populations to some extent. Further studies using the general population would be desirable.

Conclusions

The present study assessed longitudinal association between TG and other MetS components for the first time. The longitudinal association between TG and other MetS components increased with time. Among five pairs of TG and other MetS components, the correlation between TG and BMI was the largest. The correlation between TG and FPG was the smallest for men, while the correlation between TG and DBP was the smallest for women. It is important to closely monitor subjects with high levels of TG and BMI in health check-up population especially for women, because these two components are closely associated with development of hypertension, diabetes, CVD, and other chronic diseases.

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Competing Interests

The authors have declared that no competing interest exists.

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