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ORIGINAL RESEARCH

Association of Metabolic Syndrome with Aerobic Exercise and LPL rs3779788 Polymorphism in Taiwan Biobank Individuals

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Purpose: The *Lipoprotein lipase (LPL)* gene is a significant contributor to dyslipidemia. It has shown associations with several conditions including atherosclerosis, obesity, and metabolic syndrome (MetS). We assessed the interactive association between MetS and rs3779788 of the *LPL* gene based on aerobic exercise.

Materials and Methods: Data were available for 7532 Taiwan Biobank (TWB) participants recruited between 2008 and 2016. We used multiple logistic regression to determine the odds ratios (OR) for MetS and their 95% confident intervals (C.I.). Potential variables included LPL rs3779788, aerobic exercise, sex, age, education, marital status, body mass index (BMI), smoking, alcohol consumption, midnight snacking, vegetarian diet, coffee, dietary fat, and tea drinking.

Results: Aerobic exercise was protective against MetS (OR, 0.858; 95% C.I., 0.743–0.991). Compared to CC/CT genotype, the OR for developing MetS was 0.875, (95% C.I., 0.571–1.341) in TT individuals. The test for interaction was significant for the rs3779788 variant and aerobic exercise (p = 0.0484). In our group analyses, the OR for MetS was 0.841 (95% C.I., 0.727–0.974) in CC/CT and 4.076 (95% C.I., 1.158–14.346) in TT individuals who did aerobic exercise compared to those who did not.

Conclusion: Our study indicated that aerobic exercise improved metabolic syndrome in Taiwanese adults with rs3779788 CC/CT genotype relative to those with TT genotype.

Keywords: polymorphisms, variant, physical activity, metabolic disorders

Introduction

Metabolic syndrome is characterized by central obesity, hypertension, hyperglycemia, and dyslipidemia based on the guidelines of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[1] It is a general term for a group of conditions that include cardiovascular disease (CVD), coronary heart disease (CHD), and type 2 diabetes mellitus.[2,3] According to the World Health Organization (WHO), about 17.9 million people die from CVD each year. In Taiwan, CVD has been the second-leading cause of death over the last decade.[4] The mortality rate was 87.6 per 100,000 population in 2017.[5] MetS remains a major risk factor for CVDs. Due to the increasing prevalence rates and several chronic complications, MetS has become one of the major challenges of global public health.[6]

The etiology of MetS is multifactorial and includes genetic and unhealthy lifestyle factors such as smoking,[7] heavy drinking,[8] poor diet, and physical inactivity.[9] Lifestyle modification is essential in preventing MetS and related complications. Regular

exercise is known to play an important role in cardiovascular health[10] and glucose metabolism.[11] Physical activity (especially aerobic exercise) has improved dyslipidemia, insulin resistance, and obesity.[12] Inverse relationships have also been reported between vigorous exercise and cardiovascular risk factors associated with the MetS.[13] It has been estimated that physical inactivity could increase the relative risk (RR) of coronary heart disease by 6%.[14]

Aside from the lifestyle variables, genetic factors are also important in assessing risk factors associated with MetS.[15] Several polymorphisms in certain genes have been associated with both components of MetS and lifestyle interventions that include exercise.[12] One such gene is the *LPL* gene that is located on the human chromosome 8p22 and is responsible for the metabolism and transport of lipoproteins. Decreased *LPL* activity has also been associated with several diseases such as atherosclerosis, obesity, dyslipidemia, and Alzheimer's disease.[16]

Polymorphisms in the LPL gene affect not only the expression of *LPL* but also the relationship between dyslipidemia and insulin resistance.[17–19] Some of the variants in this gene have also been consistently associated with MetS risk.[20] Some of the LPL polymorphisms are protective against CAD. Genotypic frequencies of the protective polymorphisms in the *LPL* gene have significantly decreased in patients with hyperlipidemia.[21] The *LPL* gene is modulated by physical activity (PA).[22] However, it remains unclear how *LPL* expression is affected by different exercise modalities.

In Taiwan, generalized multifactor dimensionality reduction (GMDR) analyses have already been performed to show the interactive effects of *BUD13, CETP, LIPA*, smoking, and physical activity on MetS.[23] But how PA regulates MetS in people with different *LPL* polymorphisms is still not well understood. In light of this, we examined the relationship between aerobic exercise and *LPL* rs3779788 polymorphism in relation to MetS among Taiwanese adults.

Methods and Methods
Databases

This was a population-based study. Data were obtained from TWB, a national biomedical research database that contains genetic data of Taiwanese residents. Its objective is to undertake large-scale cohort and case-control studies through a combination of genetic and medical information. All methods were carried out following the relevant guidelines and regulations. Before data collection, all participants had provided written informed consent. The TWB was established in 2005. Data used in this study were collected between 2008 and 2016. The Institutional Review Board of Chung Shan Medical University approved this study (CS2-16114).

Study Participants and Definition of Metabolic Syndrome

Our study data were from 20,291 TWB participants between the ages 30 and 70. However, we excluded underweight individuals (n=633) and those with incomplete or missing values (n =12,126). Data included in the final analyses were from 7532 participants. Among them, 655 women and 779 men were identified with MetS. Metabolic syndrome was defined according to the revised NCEP/ATP III criteria proposed by the Health Promotion Administration in Taiwan.[24,25] In the revised version, the threshold for abdominal obesity had been lowered from 102 to 90 cm in Taiwanese men and 88 to 80 cm in women. Participants were defined as having MetS if they had at least three of the following conditions: (1) abdominal obesity (waist circumference: men ≥90cm, women ≥80cm); (2) hypertension (systolic blood pressure ≥130mmHg or diastolic blood pressure ≥85mmHg); (3) hyperglycemia (fasting blood glucose ≥100mg/dl); (4) low high-density lipoprotein cholesterol (men <40mg/dl, women <50mg/dl); or (5) high triglyceride (triglyceride ≥150mg/dl).

Baseline data included sex, age, education level, marital status, body mass index (BMI), and lifestyle factors like exercise, smoking (never/former and current smoker), alcohol consumption (150 cc per week or regularly for 6 months), midnight snacking (extra snack within an hour before going to bed), coffee drinking (at least three times a week) and tea drinking (at least one time per day).

Information on exercise was extracted from a self-reported questionnaire. Participants chose a maximum of three habitual exercise types. Regular exercisers were people who had at least 3 sessions of exercise a week, each session lasting for at least 30 minutes in the last three months. Aerobic exercises studied included jogging, strolling, swimming, yoga, Taijiquan, biking, aerobic dance, and ballroom dance. Participants did at most 3 types of aerobic exercises per week. We assessed dietary fat based on 12 questions (with responses to each question based on a five-point scale; 1 = never, 2 = seldom, 3 = sometimes, 4 = frequently,

and 5 = always), scored 0 to 60, with a higher score indicating greater consumption of a fat diet over the past month.

Genetic Variant Selection/Genotyping

We selected rs3779788 in the *LPL* gene after reviewing the literature. The Biobank samples had been genotyped in Academia Sinica using the custom Axiom Genome-Wide Array Plate system (Affymetrix, Santa Clara, CA, USA). The biobank samples were included in the analysis model if the call rates were greater than 10%. The rs3779788 polymorphism was in Hardy-Weinberg equilibrium (p $\geq$0.05) and the minor allele frequency (MAF) was $\geq$0.05.

Statistical Analysis

Data processing and statistical analyses were conducted using the PLINK 1.09 beta and SAS 9.4 software (SAS Institute, Cary, NC, USA). Data with normal distributions were analyzed by the Chi-square test. Normally distributed variables were presented as numbers and percentages. A p-value less than 0.05 was considered statistically significant. To estimate the genotypic association of the rs3779788 with MetS, multivariate logistic regression models were used to evaluate the genotype-specific ORs and their 95% C.I. Recessive models were used to determine the interaction between aerobic exercise and rs3779788 on MetS risk.

Results

Overall, 7532 participants met the inclusion criteria of the study (Table 1). Among participants with MetS (n = 1434), 779 were men and 655 were women. Of these participants, 1401 (97.70%) were those with rs3779788 CC/CT genotype of rs3779788 while 33 (2.30%) were those with the TT genotype. Of the 6098 individuals with no MetS, 5943 (97.46%) were those with CC/CT, and 155 (2.54%) were those with the TT genotype. There were no significant differences between participants with and without MetS based on genotype distributions (p=0.5993). After adjusting for confounders (Table 2), the odds of having MetS was significantly lower among those who did aerobic exercise regularly (OR=0.858, 95% C.I.=0.743–0.991) compared with non-exercisers. The odds ratio for MetS was 3.712 (95% C.I.= 3.122–4.414) in overweight, 13.681 (95% C.I.= 11.464–16.327) in obese compared to normal-weight individuals, 1.429

Table 1 Demographic Characteristics of Study Participants

	No MetS	MetS	p-value
	(n=6098)	(n=1434)	
rs3779788, n (%)			0.5993
CC/CT	5943 (97.46)	1401 (97.70)	
TT	155 (2.54)	33 (2.30)	
Exercise, n (%)			0.9613
No	4074 (66.81)	959 (66.88)	
Aerobic exercise	2024 (33.19)	475 (33.12)	
Sex, n (%)			<0.0001
Female	3352 (54.97)	655 (45.68)	
Male	2746 (45.03)	779 (54.32)	
Age, yr			<0.0001
30–40	1878 (30.80)	226 (15.76)	
41–50	1812 (29.71)	365 (25.45)	
51–60	1581 (25.93)	507 (35.36)	
61–70	827 (13.56)	336 (23.43)	
Education, n (%)			<0.0001
University & above	3330 (54.61)	566 (39.47)	
Senior High School	1915 (31.40)	509 (35.50)	
Junior High School	507 (8.31)	188 (13.11)	
Elementary & below	346 (5.67)	171 (11.92)	
Marital status, n (%)			<0.0001
Married	4781 (78.40)	1140 (79.50)	
Single	706 (11.58)	113 (7.88)	
Divorced	391 (6.41)	108 (7.53)	
Widowed	220 (3.61)	73 (5.09)	
BMI (kg/m^2)			<0.0001
Normal	3440 (56.41)	227 (15.83)	
Overweight	1830 (30.01)	488 (34.03)	
Obese	828 (13.58)	719 (50.14)	
Smoking, n (%)			<0.0001
Never	4793 (78.60)	994 (69.32)	
Former	663 (10.87)	199 (13.88)	
Current	642 (10.53)	241 (16.81)	
Alcohol Drinking, n (%)			<0.0001
Never	5555 (91.10)	1207 (84.17)	
Former	139 (2.28)	80 (5.58)	
Current	404 (6.63)	147 (10.25)	
Midnight snacking, n (%)			0.0118
No	4211 (69.06)	941 (65.62)	
Yes	1887 (30.94)	493 (34.38)	
Coffee drinking, n (%)			<0.0001
No	4012 (65.79)	1024 (71.41)	
Yes	2086 (34.21)	410 (28.59)	

(*Continued*)

Table 1 (Continued).

	No MetS	**MetS**	**p-value**
	(n=6098)	**(n=1434)**	
Tea drinking, n (%)			0.2507
No	3850 (63.14)	882 (61.51)	
Yes	2248 (36.86)	552 (38.49)	
Vegetarian diet, n (%)			0.2312
No	5499 (90.18)	1308 (91.21)	
Yes	599 (9.82)	126 (8.79)	
Dietary fat, mean score (SE)	32.100 ± 0.098	32.645 ± 0.202	0.0153

Note: Data were presented as numbers and percentages. CC/CT and TT are the rs3779788 genotypes.
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; yr, year.

(95% C.I.= 1.154–1.770) in current compared to nonsmokers, and 1.454 (95% C.I.= 1.042–2.030) in former compared to non-alcohol drinker. Also associated with increased odds of having MetS were the higher age groups: 41 to 50 year (OR, 1.634; 95% C.I.= 1.334–2.002), 51 to 60 year (OR, 2.724; 95% C.I.=210–3.358), and the 61–70 year age group (OR, 3.765; 95% C.I. =2.960–4.789), respectively compared to the 30 to 40 age group.

There was an interaction between rs3779788 and aerobic exercise (p=0.0484). In a separate multivariable model stratified by rs3779788 genotypes (Table 3), the ORs were 0.841 in those with the CC/CT genotype (95% C.I.=0.727–0.974) and 4.076 (95% C.I.=1.158–14.346) in those with TT genotype who were engaged in aerobic exercise compared to their inactive counterparts. In another model with the "no exercise and CC/TT" group representing the reference group (Table 4), the OR was 0.841 (95% C.I.=0.727–0.973) in aerobic exercise and CC/CT individuals. No significant differences were observed in TT individuals.

Discussion

To our understanding, our study is the first to determine the links between *LPL* variant and aerobic exercise in relation to MetS in Taiwan. We observed a significant interaction between *LPL* rs3779788 and aerobic exercise. Our stratified analyses indicated that aerobic exercise was protective against MetS in people with CC/CT but not TT genotype. Aerobic exercise is known to improve MetS by enhancing glucose transport and GLUT4 translocation.[26] However, the mechanistic bases for the links between

Table 2 Odds Ratios for MetS Among Study Participants

	OR	**95% C.I.**
rs3779788 (ref: CC/CT)		
TT	0.875	0.571–1.341
Exercise (ref: No)		
Aerobic exercise	0.858	0.743–0.991
Sex (ref: Female)		
Male	0.960	0.817–1.129
Age (ref: 30–40)		
41–50	1.634	1.334–2.002
51–60	2.724	2.210–3.358
61–70	3.765	2.960–4.787
Education (ref: University & above)		
Senior High School	1.243	1.067–1.448
Junior High School	1.388	1.111–1.732
Elementary & below	1.434	1.118–1.840
Marital status (ref: Married)		
Single	1.026	0.804–1.309
Divorced	1.238	0.958–1.958
Widowed	1.016	0.739–1.397
BMI, kg/m² (ref: Normal)		
Overweight	3.712	3.122–4.414
Obese	13.681	11.464–16.327
Smoking (ref: Never)		
Former	0.869	0.702–1.076
Current	1.429	1.154–1.770
Alcohol Drinking (ref: Never)		
Former	1.454	1.042–2.030
Current	1.256	0.988–1.598

Note: Adjusted for midnight snacking, coffee and tea consumption, vegetarian diet, and dietary fat.
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; OR, odds ratio; ref, reference.

rs3779788, aerobic exercise, and MetS remain to be determined.

Several polymorphisms of the lipoprotein metabolism-associated genes have shown significant associations with different components of MetS or related traits.[27] Among them, APOA5 rs662799,[28] BUD13 rs11216126, and rs180349,[29] CD36 rs13230419, rs13246513, rs3173804, rs7755 and rs3211850)[30] variants were associated with increased risk of MetS while CD36 rs3211938[30] and GCK rs1799884[28] appeared to be protective. *LPL* is an enzyme that promotes hydrolysis of lipoprotein and regulates various aspects of metabolism, such as energy balance, insulin action, body weight regulation, and

Table 3 Odd Ratios for MetS Among Individuals with Rs3779788 Genotypes

	CC/CT		TT	
	OR	**95% C.I.**	**OR**	**95% C.I.**
Exercise (ref: No)				
Aerobic exercise	0.841	0.727–0.974	4.076	1.158–14.346
Sex (ref: Female)				
Male	0.986	0.838–1.161	0.105	0.022–0.507
Age (ref: 30–40)				
41–50	1.620	1.320–1.988	2.334	0.416–13.092
51–60	2.702	2.187–3.338	3.836	0.624–23.573
61–70	3.639	2.852–4.642	17.570	2.466–125.193
Education (ref: University & above)				
Senior High School	1.243	1.065–1.451	1.142	0.331–3.948
Junior High School	1.389	1.110–1.738	2.775	0.375–20.545
Elementary & below	1.487	1.155–1.914	0.731	0.078–6.889
Marital status (ref: Married)				
Single	1.006	0.785–1.289	2.369	0.413–13.594
Divorced	1.234	0.954–1.597	1.098	0.086–14.033
Widowed	1.068	0.773–1.475	0.169	0.012–2.368
BMI, kg/m^2 (ref: Normal)				
Overweight	3.753	3.149–4.473	2.607	0.740–9.185
Obese	13.684	11.439–16.370	42.519	9.291–194.577
Smoking (ref: Never)				
Former	0.857	0.691–1.064	3.021	0.400–22.809
Current	1.399	1.128–1.737	25.386	2.747–234.632
Alcohol Drinking (ref: Never)				
Former	1.515	1.082–2.121	0.130	0.005–3.150
Current	1.256	0.984–1.604	0.726	0.100–5.291

Note: Adjusted for midnight snacking, coffee and tea consumption, vegetarian diet, and dietary fat.
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; OR, odds ratio; ref, reference.

atherosclerosis.[31] The *LPL* gene spans about 30 kb that is located on chromosome 8p22 and consists of 10 exons and 9 introns.[32] This gene is primarily expressed in the heart, muscle, and adipose tissue.[33] Several mutations were found in the *LPL* gene which could cause *LPL* deficiency.[34]

Several studies have shown that polymorphisms of the *LPL* gene may occur in at least 88 locations in the human DNA and mutations could change the role and function of the LPL enzyme related to MetS risk.[32,35–37] A study indicated that about 20% of patients with hypertriglyceridemia are carriers of common *LPL* gene mutations associated with hyperlipidemia (HLP).[38] Studies with the young Asian Indian population reported significant associations between *LPL* gene polymorphisms (rs1800590) and MetS, and the frequency of the minor allele (G) was higher in patients with MetS (OR, 2.72; 95% CI, 1.07–8.16).[35] Besides, genetic variants of the *LPL* promoter are associated with the alternation in lipid metabolism which may lead to obesity and type 2 diabetes.[36,37,39] In the Framingham Offspring Study, both rs1801177 and rs268 variants in the *LPL* gene were associated with changes in lipoprotein and increased risk of atherosclerosis.[40] A few studies found that rs3779788 SNP in the *LPL* gene was related to coronary artery disease and blood lipid.[41,42]

Physical inactivity has been associated with certain unhealthy effects worldwide: it could lower LCAT (lecithin-cholesterol acyltransferase) which transfers free fatty acids to HDL.[14,43] Different types of exercise will influence the human body in various ways. For instance, low-to-moderate intensity cardiorespiratory exercise was reported to improve components of MetS in

Table 4 Odds of Having MetS Based on Aerobic Exercise and Rs3779788 Genotypes

	OR	95% C.I.
Aerobic exercise and rs3779788 (ref: no exercise and CC/CT)		
No exercise and TT	0.636	0.366–1.107
Aerobic exercise and CC/CT	0.841	0.727–0.973
Aerobic exercise and TT	1.282	0.659–2.496
Sex (ref: Female)		
Male	0.957	0.815–1.125
Age (ref: 30–40)		
41–50	1.634	1.334–2.001
51–60	2.722	2.209–3.356
61–70	3.765	2.960–4.789
Education (ref: University & above)		
Senior High School	1.243	1.067–1.448
Junior High School	1.395	1.117–1.742
Elementary & below	1.441	1.122–1.850
Marital status (ref: Married)		
Single	1.028	0.806–1.312
Divorced	1.236	0.957–1.596
Widowed	1.010	0.734–1.389
BMI, kg/m² (ref: Normal)		
Overweight	3.720	3.128–4.423
Obese	13.722	11.497–16.377
Smoking (ref: Never)		
Former	0.873	0.705–1.081
Current	1.439	1.162–1.783
Alcohol Drinking (ref: Never)		
Former	1.467	1.051–2.048
Current	1.257	0.988–1.599

Note: Adjusted for midnight snacking, coffee and tea consumption, vegetarian diet, and dietary fat.
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; OR, odds ratio; ref, reference.

postmenopausal women.[44] Dynamic endurance training also has beneficial effects on MetS-related risk factors.[13] Many studies found that aerobic exercise played an essential role in decreasing MetS risk.[45–47] In a previous study, resistance exercise helped lower MetS risk, independent of aerobic exercise.[48] However, according to other researchers, the decrease in MetS risk is more substantial when aerobic exercise is combined with resistance exercise.[48–50]

In our primary analysis, we found that aerobic exercise was protective against MetS (OR=0.858; 95% C.I., 0.743–0.991). However, after stratification by rs3779788 genotypes, we realized that the odds for MetS were lower among CC/CT (OR= 0.841; 95% C.I., 0.727–0.974) but not TT individuals (OR= 4.076; 95% C.I., 1.158–14.346). In other words, the association between Mets and exercise differed across the rs3779388 genotypes. However, the mechanisms behind these associations are not fully understood. More studies are needed to support these findings. In the current study, we also found that well-known risk factors such as older age, obesity, overweight, and smoking were associated with increased odds of having MetS.

Of note, we acknowledge the following limitations. First, causal conclusions could not be drawn considering that the study design is observational. Second, we collected our lifestyle data using self-reported questionnaires. This may have introduced recall bias. Next, our database contained no information on exercise intensity, saturated fatty acids, trans-fatty acids, simple carbohydrates, and medication history.

Conclusion

In conclusion, we observed a relationship between MetS and an *LPL* variant (rs3779788) among Taiwanese adults 30 to 70 years old. We found that aerobic exercise was protective against MetS among those with the rs3779788 CC/CT genotype compared to those with TT genotype.

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Disclosure

The authors report no conflicts of interest in this work.

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