



Apolipoprotein B is associated with metabolic syndrome in Chinese families with familial combined hyperlipidemia, familial hypertriglyceridemia and familial hypercholesterolemia

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Abstract

There is a paucity of data concerning the metabolic syndrome (MetS) in families with familial combined hyperlipidemia (FCHL), familial hypertriglyceridemia (FHTG), familial hypercholesterolemia (FH) and normolipidemic families in China. This study investigated the prevalence of MetS in these families and explored potential factors relevant to MetS. We recruited 70 families with 560 individuals ≥ 20 years of age, including 43 FCHL families with 379 individuals, 3 FHTG families with 30 individuals, 16 FH families with 102 individuals and 8 normolipidemic families with 49 individuals. The definition of MetS is determined using modified criteria of National Cholesterol Education Program substituting body mass index for waist circumference. MetS is identified in 60.7% of FCHL patients and 71.4% of FHTG patients. The prevalence of MetS in family members is 36.7% for FCHL, 33.3% for FHTG, 17.6% for FH and 16.3% for normolipidemic families, with an odds ratio (OR) of 2.97 (95% CI 1.29–7.07, $P=0.007$) in FCHL families compared with normolipidemic families. Apolipoprotein B (apoB) is associated with MetS by multiple logistic analysis with an OR of 1.05 (1.03–1.07, $P<0.001$) in FCHL families, OR of 1.26 (1.03–1.55, $P=0.026$) in FHTG and OR of 1.07 (1.01–1.12, $P=0.014$) in FH families, independent of variables including age, gender, apolipoprotein A1, and low density lipoprotein cholesterol. Apolipoprotein A1 provided an OR of 0.95 (0.94–0.97, $P<0.001$) in FCHL families and OR of 0.94 (0.90–0.97, $P=0.011$) in FH families, but neither in FHTG nor in normolipidemic families (both $P>0.05$). Thus, apoB may be regarded as a relevant factor in the assessment of MetS in FCHL, FHTG and FH families. However, this finding needs to be verified by prospective studies in diverse ethnicities and warrants additional studies to elucidate possible mechanisms linking apoB to MetS.

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1. Introduction

The metabolic syndrome (MetS), early description of “syndrome X” by Reaven [1], is defined as the clustering of risk factors for cardiovascular disease that includes insulin resistance, abdominal obesity, elevated triglyceride,

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hypertension and low high density lipoprotein cholesterol (HDL) [2,3]. Isomaa and his colleagues [4] showed that individuals with MetS were at a three-fold greater risk of coronary heart disease and stroke, and more than a five-fold greater risk of cardiovascular mortality. Recently, the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) put forth a definition for MetS [5]. An important feature of their recommendation is its easy to use in clinical practice [6], compared with earlier definitions of MetS available from the World Health Organization [7]. It has been estimated that the prevalence of MetS as defined by NCEP-ATP III definition is 24% of individuals in the U.S. who are at least 20 years of age and exceeds 40% of the population older than 40 years of age [8]. Cheng shows that the prevalence of MetS is 13.3% in general populations in China [9].

How MetS occurs is unclear. Many researchers agree that insulin resistance plays a central pathophysiological role in the clustering of cardiovascular risk factors in the development of MetS [1,10]. However, the epidemic of MetS has most likely been triggered by environmental factors, immunity and inflammation [3]. A prior study demonstrated that obesity was the principal reason for the increased prevalence of MetS in China [11]. Moreover, dyslipidemia is a hallmark of MetS and is characterized by elevation of triglyceride and low HDL [12] and plasma low density lipoprotein cholesterol (LDL) levels are often normal in patients with MetS [3].

In the early 1970s, Goldstein et al. [13] ascertained that familial combined hyperlipidemia (FCHL), familial hypertriglyceridemia (FHTG) and familial hypercholesterolemia (FH) appeared to be risk factors for coronary heart disease. The familial forms of FCHL and FHTG are common among families with coronary heart disease [14]. Recently, Hopkins et al. [15] showed that the risk of coronary artery disease in FCHL and FHTG was related to feature of the MetS. The MetS was identified in 65% of FCHL and 71% of FHTG patients compared with 19% in controls without FCHL or FHTG [15]. Apolipoprotein B (apoB) elevation was a major characteristic of individuals with FCHL [16]. Some evidence showed that apoB and apolipoprotein (apoA1) could be superior to LDL and HDL as predictors of vascular risk [17,18]. Sattar et al. suggest that apoB is a better candidate risk parameter than non-HDL for identifying a subgroup of individuals with or without MetS with elevated cardiovascular risk [19]. It is on the basis of the above-mentioned observations that NCEP-ATP III has stated that apoB and non-HDL are clinically equivalent [5]. However, there is a paucity of data concerning the MetS across families with FCHL, FHTG, FH and normolipidemic families in China. In this investigation, we examined the prevalence of MetS in different familial forms of hyperlipidemia and further explored possible predictors of MetS in China.

2. Methods

2.1. Collection of families and study design

We have developed a successful, effective approach for recruiting families of patients with lipid disturbances through genetic field work in our hospital on the basis of the method of Schuster et al. [20]. Briefly, if a person is less than 60 years of age and has a total cholesterol (TC) and/or triglyceride level equal to or exceeding the 95th percentile of persons on the hospital ward of the hospital or in the outpatient clinics by his physicians, the patient would be informed that his condition is likely to be familial and invited to participate in the family studies. If the index patient agrees, he would be responsible for recruiting family members on the basis of his/her family tree. Most of all surveys were done in local hospitals and only some of the family members were recruited at home. All participants completed a health questionnaire and submitted a fasting blood sample, from which we measured lipid values and extracted DNA for future genetic analysis. Moreover, we also extended our genetic field work to three collaborative medical centers in Shandong, Henan and Hebei Provinces in northern China. Investigators trained the physicians and assistants who took part in the study. Individuals with hepatic, renal or thyroid disorders were excluded from this study. Additionally, we recruited some family members who did not have dyslipidemia as controls from the same area. Informed consent was obtained from all participants in this survey. Altogether, the compliance of family members was 81.4%. The family study had been approved by the Ethics Committee of Peking Union Medical College.

2.2. Measurement of lipids and other phenotypes

Plasma was available by centrifuge method within three hours of phlebotomy. Plasma lipids and glucose were measured centrally by fully automated techniques. We measured concentrations of TC, HDL and triglyceride by enzymatic techniques, apoA1 and apoB by immunoturbidimetry. All measurements were done with fresh plasma, and reagents were always from the same manufacturer. LDL was estimated by means of the Friedewald formula [21], provided that the triglyceride values were less than 400 mg/dl. If the triglyceride value was 400 mg/dl or over, LDL was measured using the Lipid Research Clinic beta quantification method.

2.3. Diagnosis criteria of different hyperlipidemia

A person was diagnosed as having hyperlipidemia when he met the criteria of TC and/or triglyceride in the excess of the 95th percentile for age and gender [22] or the current use of anti-hyperlipidemic medication.

Families with FCHL met each of the following criteria: first, at least two consanguine relatives with a primary

elevation of TC and/or triglyceride within a same family (Fredrickson classification IIa, IIb, or IV); second, absence of secondary causes of hyperlipidemia (renal or hepatic insufficiency, hypothyroidism, and medication), absence of the apolipoprotein E2/E2 genotype and tendon xanthomas [13].

Families with FHTG met each of the following criteria: first, at least two consanguine relatives with a primary elevation of triglyceride within a same family; second, absence of secondary causes of hyperlipidemia (renal or hepatic insufficiency, hypothyroidism, and medication) [13].

Families with FH met each of the following criteria: first, at least two consanguine relatives with a primary elevation of TC within a same family (type IIa); second, absence of secondary causes of hyperlipidemia (renal or hepatic insufficiency, hypothyroidism, and medication) [13]; third, presence of skin or tendon xanthomas [13].

Normolipidemic families met the following criteria: any consanguine relative without primary elevations of TC and triglyceride within a same family.

2.4. Definition of the MetS

MetS was diagnosed according to the NCEP definition [5]. An individual was deemed to have the MetS if three or more of the following criteria were satisfied: 1) waist circumference >102 cm in men and >88 cm in women; 2) triglyceride \geq 150 mg/dl; 3) HDLC <40 mg/dl in men and <50 mg/dl in women; 4) Blood pressure \geq 130/85 or known treatment for hypertension; 5) fasting glucose level \geq 110 mg/dl or known treatment for diabetes. Since waist circumference was not available in this study. We used

Chinese cutpoint for abdominal obesity as body mass index (BMI) \geq 25.0 kg/m² in men and \geq 24.0 kg/m² in women, instead of corresponding cutpoint for central obesity with waist circumference \geq 85 cm in men and \geq 80 cm in women [23–25].

2.5. Statistical analysis

All statistical analyses were performed with SPSS statistical software (SPSS Inc). Distributions of phenotypes were test for normality. Analysis of variance was used to assess differences in means of continuous variables. Analysis of covariance using the general linear model procedure was used to adjust the variables for age. Significance of univariate odds ratio (OR) was determined by the chi-square test. To evaluate the independent determinants of MetS, multiple logistic regression analysis was used to test whether MetS was associated with other risk factors, including age, gender, apoA1, apoB, LDLC in FCHL, FHTG, FH, normolipidemic families and combined families (FCHL, FHTG, FH and normolipidemic families), respectively. All probability values were based on two-sided tests of statistical significance. Significance was considered at the 5% level.

3. Results

We recruited 70 different families with a total of 560 participants \geq 20 years of age. Among these families, there were four different types as follows: 43 FCHL families with 379 participants, 3 FHTG families with 30 participants, 16 FH families with 102 participants and 8 normolipidemic

Table 1

Age-adjustment means of individuals with or without metabolic syndrome in different families among adults aged \geq 20 years (mean \pm SD)

	FCHL		FHTG		FH		NF	
	Without MetS	With MetS	Without MetS	With MetS	Without MetS	With MetS	Without MetS	With MetS
No. of families	10	33 ^a	0	3 ^a	11	5 ^a	6	2 ^a
No. of subjects	240	139	20	10	84	18	41	8
Sex (M/F)	94/146	86/53	7/13	6/4	44/40	9/9	21/20	1/7
Age (yrs)	40.44 \pm 13.06*	50.40 \pm 13.73	37.30 \pm 12.77*	49.60 \pm 10.52	44.32 \pm 13.75*	53.28 \pm 11.36	43.07 \pm 14.21*	55.75 \pm 12.38
TC (mg/dl)	191.53 \pm 44.52	224.08 \pm 56.83	152.23 \pm 33.32	179.04 \pm 39.06	213.70 \pm 44.36	239.65 \pm 44.19	173.24 \pm 29.70	170.97 \pm 38.32
TG (mg/dl) ^b	118.55 \pm 94.37	291.20 \pm 213.05	98.95 \pm 67.40	249.76 \pm 265.79	87.44 \pm 32.59	149.65 \pm 41.83	76.33 \pm 4.58	110.89 \pm 42.55
LDLC (mg/dl)	120.95 \pm 38.56*	142.86 \pm 56.21	89.00 \pm 25.76	98.65 \pm 23.76	145.77 \pm 42.39*	170.61 \pm 40.67	111.56 \pm 27.47	108.48 \pm 34.55
HDLC (mg/dl) ^b	47.34 \pm 11.95	34.40 \pm 7.55	43.44 \pm 7.31	32.68 \pm 9.66	50.43 \pm 13.27	39.10 \pm 6.41	46.40 \pm 9.67	40.31 \pm 6.28
ApoA1 (mg/dl)	121.74 \pm 17.70 [†]	112.87 \pm 14.04	112.29 \pm 14.22	103.12 \pm 14.12	112.40 \pm 17.57	106.23 \pm 14.44	121.56 \pm 14.86	118.91 \pm 11.59
ApoB (mg/dl)	79.62 \pm 21.13 [†]	97.29 \pm 21.06	65.71 \pm 18.54*	80.14 \pm 14.31	72.48 \pm 18.61*	90.31 \pm 17.59	75.13 \pm 16.25	73.63 \pm 25.42
BMI (kg/m ²) ^b	23.23 \pm 3.01	27.20 \pm 2.74	23.97 \pm 2.46	27.02 \pm 2.50	22.79 \pm 3.09	26.86 \pm 3.84	23.81 \pm 3.54	28.23 \pm 2.39
SBP (mm Hg) ^b	115.05 \pm 18.53	135.99 \pm 23.85	115.22 \pm 11.75	131.78 \pm 16.26	116.72 \pm 14.19	138.06 \pm 30.67	123.82 \pm 21.06	153.25 \pm 24.93
DBP (mm Hg) ^b	77.12 \pm 10.58	89.25 \pm 12.75	78.33 \pm 7.52	88.22 \pm 10.56	76.18 \pm 8.12	83.44 \pm 9.04	83.72 \pm 9.26	92.00 \pm 7.41
Glucose (mg/dl) ^b	97.12 \pm 12.24	112.97 \pm 39.09	48.58 \pm 28.03	57.48 \pm 57.92	81.07 \pm 17.17	110.45 \pm 60.30	84.65 \pm 19.42	77.08 \pm 27.64

*: $P < 0.05$, [†]: $P < 0.001$: compared with MetS group in the same families.

FCHL: familial combined hyperlipidemia.

FHTG: familial hypertriglyceridemia.

FH: familial hypercholesterolemia.

NF: normalipidemic families.

^a At least two persons met the criterion of affected for metabolic syndrome in each family.

^b Not available for comparisons of means because criteria for selection of cases are based on these parameters.

Table 2
Feature of metabolic syndrome in different dyslipidemic families and normolipidemic families among adults aged ≥ 20 years

	FCHL (%)	FHTG (%)	FH (%)	NF (%)
Abdominal obesity	50.8	62.1	36.6	47.9
Hypertriglyceridemia	40.3	26.7	16.7	2.0
Low HDL cholesterol	64.8	73.3	44.1	51.0
High blood pressure	30.9	26.7	22.5	44.9
High fasting glucose	13.8	3.3	6.9	4.1

Abbreviations as in Table 1. See Methods for a description of the 5 criteria of the metabolic syndrome.

families with 49 participants. The clinical characteristics of the study population are shown in Table 1. Means of age-adjusted apoB in participants with MetS were significantly higher than in participants without MetS in dyslipidemic families (all $P < 0.05$). Moreover, the LDLC was found to be significantly higher in patients with MetS, compared to participants without MetS in either FCHL or FH families (all $P < 0.05$). This was not significant for FHTG and normolipidemic families (all $P > 0.05$). Meanwhile, apoA1 level was significantly lower in patients with MetS, compared with participants without MetS in FCHL families ($P < 0.05$) and there was also a lower tendency in other families, which was not statistically significant. FHTG and FCHL families had the largest number of families with at least two affected relatives with MetS (Table 1).

Family members with FCHL or FHTG had the highest prevalence of abdominal obesity, hypertriglyceridemia and low HDLC concentration (Table 2). FCHL members had the highest prevalence of high fasting glucose. 60.7% (108/178) of all FCHL patients and 71.4% (5/7) of all patients FHTG met the criteria for MetS ($P = 0.70$, comparing FCHL and FHTG). Furthermore, FCHL and FHTG members had the highest prevalence of MetS. Overall, the crude prevalence of MetS was highest among FCHL members (36.7%), was similar in FHTG members (33.3%) and was lowest among FH members (17.6%) and normolipidemic families (16.3%). These observations suggest that metabolic profiles of FCHL and FHTG are remarkably similar to each other. FCHL to normolipidemic families had an odds ratio

(OR) for MetS of 2.971 (95% CI 1.291–7.073, $P = 0.007$) (36.7% vs 16.3%).

In order to examine the risk factors relevant to MetS, we performed multiple logistic analysis with age, gender, apoA1, apoB and LDLC as covariables in FCHL, FHTG, FH, normolipidemic families and combined families, respectively (Table 3). Age was a significant risk factor for MetS in each kind of family (all $P < 0.05$), even in combined families. ApoB is a positive predictor for MetS in each type of hyperlipidemic family (all $P < 0.05$), with adjusted OR of 1.052 (1.034–1.070) in FCHL families, OR of 1.261 (1.028–1.547) in FHTG families, OR of 1.066 (1.013–1.122) in FH families and OR of 1.064 (1.048–1.080) in combined families, but it is not available in normolipidemic families ($P > 0.05$). Furthermore, a negative predictor for MetS also could be available in apoA1 among FCHL, FH and combined families (all $P < 0.05$, Table 3). Surprisingly, entering LDLC was not associated with MetS in any kind of family, however, a negative significant association could be observed in combined families ($P < 0.001$), with adjusted OR of 1.064 (1.048–1.080) (Table 3).

4. Discussion

The prevalence of MetS has reached epidemic proportion [10]. Recent observations stress the importance of identifying individuals with MetS for the development of diabetes and cardiovascular disease [5,8,26]. Furthermore, the MetS is a common phenomenon in modern China [9,27]. To our knowledge, this is the first study reporting the association of the MetS using modified NCEP definition in Chinese families with FCHL, FHTG and FH.

The major finding of this study is that apoB is an important marker to segregate individuals with MetS in FCHL, FHTG and FH families. Meanwhile, we were able to show that age was a risk factor for MetS in each group, which is consistent with the results of previous researches [8]. In contrast, apoA1 is a negative predictor for MetS in families with FCHL and FH, but neither in FHTG nor in normolipidemic families. Maybe it is due to sample size of families with FHTG in this study. Other studies demonstrated that apoA1 may provide

Table 3
Adjusted odds ratios for metabolic syndrome with multiple logistic regression in different and combined families among adults aged 20 years

	FCHL		FHTG		FH		NF		Combined families	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age (yrs)	1.045 (1.026–1.065)	<0.001	1.238 (1.010–1.570)	0.049	1.047 (1.002–1.095)	0.042	1.083 (1.017–1.153)	0.013	1.048 (1.031–1.065)	<0.001
ApoA1 (mg/dl)	0.951 (0.935–0.968)	<0.001	0.903 (0.796–1.024)	0.113	0.943 (0.902–0.986)	0.011	0.970 (0.910–1.034)	0.347	0.951 (0.937–0.965)	<0.001
ApoB (mg/dl)	1.052 (1.034–1.070)	<0.001	1.261 (1.028–1.547)	0.026	1.066 (1.013–1.122)	0.014	1.010 (0.942–1.082)	0.789	1.064 (1.048–1.080)	<0.001
LDLC (mg/dl)	0.993 (0.986–1.000)	0.059	0.928 (0.857–1.004)	0.061	0.999 (0.977–1.021)	0.894	0.977 (0.935–1.021)	0.298	0.987 (0.980–0.993)	<0.001

Abbreviations as in Table 1.

Combined families: families with FCHL, FHTG, FH and NF.

more information than HDLC levels in the assessment of ischemic heart disease risk in men [28]. Additionally, LDLC is correlated with MetS in all families, but not in FCHL, FHTG, FH and normolipidemic families, respectively. Previous studies show evidence that apoB and apoA1 are superior to LDLC and HDLC as predictors of vascular risk [17,18]. Prospective data indicated that apoB was most strongly associated with ischemic heart disease even after adjustment for TC and triglyceride levels [29] and also as an index of the change in coronary stenosis [18]. Sattar et al. suggest that apoB is a better candidate risk parameter than non-HDLC for identifying a subgroup of individuals with or without MetS with elevated cardiovascular risk [19]. Moreover, apoB has been shown to be superior to non-HDLC in its association with increased carotid artery intima-media thickness in patients with FCHL [30]. Along with aforementioned studies, our observations provide substantial evidence for identifying an association of apoB with MetS in families with these lipid disorders. However, we have to point out that the association in the FCHL families is relatively weak in this study.

Our findings are that a large percentage of patients with FCHL (60.7%) and with FHTG (71.4%) also met diagnostic criteria for MetS in comparison with those without FCHL or FHTG. We believe that this is a better reflection of the true prevalence of the MetS in dyslipidemic families in Chinese. These figures were comparable with only one previous study showing that FCHL and FHTG appear to be more alike than different in their prevalence of MetS [15]. Thus, the large number of individuals with FCHL and FHTG has important implications for MetS. Although the genetic differences between FCHL and FHTG are not fully understood [14], we were able to identify that FCHL was linked to chromosome 1q in Chinese and German populations [31]. Consistent with previous reports [32], individuals with FHTG have the largest percentage of low HDLC. Furthermore, families with FH may be similar to normolipidemic families in their metabolic profile. In accordance with other studies [2,8], we found that the prevalence of MetS increases with age in all four different families in this study. The prevalence of MetS was highest in families with FCHL or FHTG, followed by FH and lowest in the normolipidemic families. Our observations revealed that the prevalence of MetS in normolipidemic families was roughly similar to that of other reports as follows: 13.3% in Chinese population from mainland China [9], 14.8% in Chinese Singaporeans [2] and 11% in Chinese Canadians [27]. One reason for the difference among some studies was that decreasing central obesity criteria resulted in increasing the prevalence of the MetS in Chinese populations. However, central obesity alone is insufficient to diagnose the MetS [2]. Of note, people of Chinese origin have the lowest MetS prevalence, compared to either South Asians [2] or Americans [8]. The differences in MetS prevalence in diverse populations may be due to the considerable heterogeneity [2,3].

The pathogenetic mechanism of MetS is unclear [26]. Family studies suggest a complex but significant genetic basis to individual components of MetS [3]. Most evidence appears to show that insulin resistance may be the underlying cause of many, but perhaps not all MetS [6,26,33]. The epidemic of MetS has most likely been triggered by environmental factors, immunity and inflammation second to genetic predisposition [10,34]. Evidence for the importance of inflammation is suggested by the fact that C-reactive protein is correlated with MetS [6,35]. Recently, Lee et al. [34] suggested that the ACE I/D polymorphisms were involved in the pathophysiology of MetS in Chinese patients with type 2 diabetes. Moreover, because of the prevalence of diabetes and obesity has risen dramatically in many countries [6,36], this will inevitably result in increasing prevalence of MetS worldwide.

Limitations of this study should be recognized. First, as we utilized measures of BMI instead of waist circumference, it is possible we have misclassified some individuals that would have been classified differently on the basis of the waist circumference measures as used in the primary NCEP definition of MetS [5]. Some data have shown that both BMI and waist circumference increase risk of cardiovascular disease and diabetes [37], but this remains controversial because some investigators have found that BMI predicts diabetes better than waist circumference [38], whereas others have found the reverse [39]. Most physicians routinely assess BMI, and waist measurement in clinical practice has not been widely used. Previous studies confirmed that some Chinese populations with a low BMI had a higher percentage of body fat than White and European populations [37,40]. The BMI cut-off point for observed risk in different Asian populations varies from 22 to 25 kg/m² [37]. Thus, we believe that the standard of cut-off points in this study is valid because other work has shown that the prevalence of hypertension, diabetes, dyslipidemia, and clustering of risk factors all increase with increasing BMI even at indices below 25 kg/m² in Chinese populations [41]. Second, there are only three families with FHTG in this study. Notably, the number of FHTG subjects is small compared with other two types of familial hyperlipidemia. However, the recruitment of families is consecutively taken, not a random design for general populations. Thus it is insufficient to spread our observations. Third, our data support the notion that apoB is an important marker for MetS in families with FCHL, FHTG and FH. However, since this study is cross sectional in design, the speculation derived from our observation is hypothesis generating rather than hypothesis proving.

In summary, we have found a novel association of apoB with MetS in hyperlipidemic families. Additionally, other studies demonstrated that the level of apoB in persons on statin treatment remains predictive of outcome, whereas that of LDLC generally does not [17]. It appears that apoB concentrations are elevated, then coronary heart disease risk can be considered high [19]. Accordingly, we speculate that apoB may provide a new insight as a relevant factor in the

assessment of MetS in Chinese families with FCHL, FHTG and FH. However, this finding needs to be verified by prospective studies or in diverse ethnicities and there is also a need for additional studies to elucidate possible mechanisms of the relationship between apoB and MetS.

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