Original Article

Recurrence Risk Ratio of Siblings and Familial Aggregation of the Metabolic Syndrome among Tehranian Population

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Abstract

Background: In this study, we aimed to determine the extent of possible genetic influence on cardio-metabolic risk factors, evaluate the familial aggregation of MetS and estimate the siblings' recurrence risk ratios in a Tehrani population.

Methods: In a cross-sectional observational study, we made anthropometric, blood pressure, and biochemical measurements in each member of 566 Tehrani nuclear families.

Results: Grandmothers had the highest incidence of atherosclerotic risk factors. Four factors were found which accounted for 77.7% of the overall variance. Recurrence risk ratio among siblings was 5.61 (95% confidence interval [CI]: 3.15–9.97). The adjusted odds ratio (OR) of proband's MetS status was 1.33 (95% CI: 1.06–1.67). The adjusted OR for the four factors to predict MetS were all significant, with obesity having the highest risk (OR: 7.50, CI: 5.91–9.52), followed by dyslipidemia/hyperglycemia (OR: 4.86, CI: 4.03–5.87), and blood pressure (OR: 4.20, CI: 3.51–5.02).

Conclusion: A high risk of MetS (five-fold) was found in siblings with MetS proband. Moreover, findings confirm the importance of obesity for the aggregation of MetS by nearly seven-fold in the study population.

Key words: Familial aggregation, metabolic syndrome, recurrence risk ratio, TLGS

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Introduction

Metabolic syndrome (MetS) is defined by a cluster of risk factors (hyperglycemia, hypertension, dyslipidemia, and abdominal obesity) that directly increase the risk of cardiovascular diseases (CVD), diabetes mellitus type 2 (DMT2), and cancer.[1] Mechanisms of MetS etiology are complex; however, genetic and environmental factors such as lifestyle changes, diet and physical inactivity are among the important factors for the pathogenesis of MetS.[2]

Genetic studies of MetS pose a great challenge, due to its complex traits and the possible manifestation of atherosclerosis traits. The prevalence of MetS varies among different ethnic groups[3–5] due to reasons not well understood. Besides variations in environmental factors, an increased genetic susceptibility may explain the observed differences.

The family is one of the most important factors affecting metabolic risk factors in children, because the family displays an interaction between genetic and shared environmental factors.[6] Familial aggregation is the clustering of certain traits, behaviors, or disorders within a given family. Family aggregation may arise because of genetic or environmental similarities. Studies estimate the increased risk of disease in relatives of affected probands, or the risk to an individual given his or her family history.[7] There have been quantitative genetic studies conducted on MetS traits, and in the Framingham family study the sibling's recurrence risk ratios were two-fold.[8] Tracking cardiovascular disease from childhood to adulthood suggests that detection of individuals at risk, along with family-based intervention programs, may have long-term benefits for the prevention of cardiovascular risks.[9] However, there were significant familial correlation coefficients in siblings up to 0.4.[10] The heritability of MetS components was very high, up to 70%, in data pertaining to twins.[11] Our previous study on MetS and its components also showed significant heritability among Tehrani population,[12] indicating strong contribution of genetic factors.

Since family studies are well suited to investigate the genetic architecture underlying the MetS, different distribution of familial aggregation status in different population, and given the lack of West Asian studies on this issue, the aim of this study was to investigate the extent of genetic influence on cardio-metabolic risk factors. In this study, we aimed to evaluate familial aggregation of MetS and to estimate the sibling's recurrence risk ratios in a Tehrani population.

Material and Methods

Study population and study design

This family-based study was conducted on families [partici-

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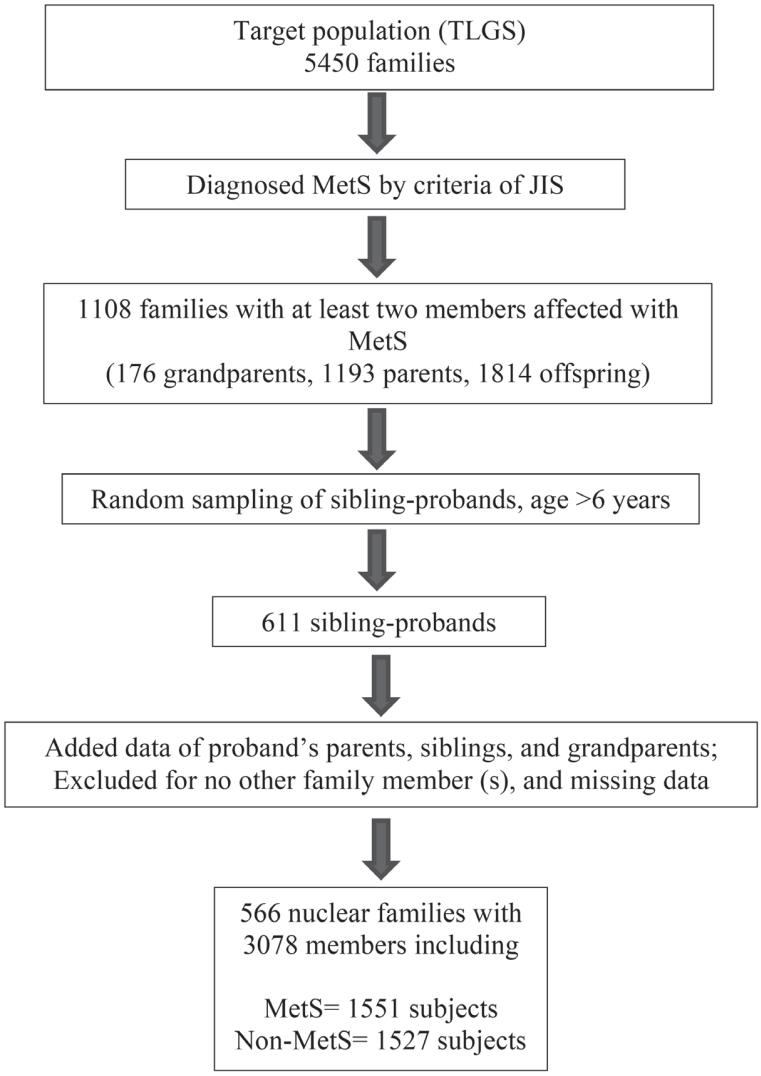

Figure 1. Study design of sibling probands study on the metabolic syndrome. MetS= 38.2%; Non-MetS= 58.5%; Missing= 3.3%

pants of Tehran Lipid and Glucose Study (TLGS)] with at least two members affected with MetS. The design of TLGS includes two major components: a cross-sectional prevalence study of cardiovascular disease and associated risk factors and a prospective 20-year follow up in several phases: phase I 1999–2001, phase II 2002–2005, and phase III 2006–2008 at approximately 3 year intervals. In the present study, families were recruited from phase III of TLGS.[13]

Figure 1 shows a flow chart of the overall study design that yielded 566 families of sibling probands (1551 subjects with MetS and 1527 subjects without MetS). Participants provided written inform consent and the study was approved by the institutional ethics committee of the Research Institute for Endocrine Sciences affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. Information on age, sex, and demographics was collected using a standardized questionnaire.

Anthropometric and blood pressure measurements

Body mass index (BMI) was calculated as weight (Kg) divided by height (m^2). Waist circumference (WC), measured at the umbilical site using an outstretched tape meter, was recorded to the nearest 0.1 cm. Systolic and diastolic blood pressures (SBP and DBP) were measured in the sitting position with a standard mercury sphygmomanometer on the left arm after at least 10 min of rest.

Blood sampling and analytic methods

Blood samples were taken in a standard sitting position after 12–14 hr of overnight fasting for biochemical analysis, and then centrifuged within 45 min of collection. Serum samples were stored at -70°C, prior to the batch assay using standard enzymatic tests for triglycerides (TG), total cholesterol (TC), and precipitation methods for low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Blood glucose was measured by the glucose oxidase method (Glucose kit; Pars Azmun, Tehran, Iran). TG and TC levels of the samples were determined by enzymatic colorimetric method (TG and TC kit; Pars Azmun, Tehran, Iran). HDL-C was determined by precipitation and enzymatic colorimetric methods (HDL-C kit; Pars Azmun, Tehran, Iran). LDL-C concentrations in samples were calculated using Friedewald's equation.[14] Coefficients of variation (CV) for TC, HDL-C and TG measurements were all below 5%.

Table 1. Characteristics of various types of metabolic syndrome and its components among family members, specified by generation and gender.

Variables	Grandfather (n = 15)	Grandmother (n = 61)	Father (n = 581)	Mother (n = 607)	Sons (n = 1009)	Daughters (n = 805)
Age (years)	73.7 ± 8.5†	69.0 ± 7.7	56.3 ± 10.2	49.6 ± 9.2‡	24.7 ± 9.3	23.3 ± 9.1‡
Total cholesterol (mg/dL)	190.6 ± 25.9	213.8 ± 44.2	194.3 ± 34.4	206.9 ± 39.6‡	169.4 ± 36.2	166.3 ± 33.9
LDL-cholesterol (mg/dL)	120.3 ± 29.5	131.5 ± 41.7	121.4 ± 29.1	129.5 ± 33.2‡	102.8 ± 30.9	101.1 ± 28.7
Waist circumference (cm)	100.7 ± 8.3	99.4 ± 12.5	99.6 ± 9.3	97.6 ± 11.5†	89.8 ± 15.1	76.2 ± 12.6‡
Body mass index (Kg/m^2)	28.4 ± 3.5	29.9 ± 5.4	28.1 ± 3.7	31.3 ± 4.6‡	25.6 ± 5.5	24.2 ± 5.2‡
Systolic blood pressure (mmHg)	131.7 ± 16.2	132.6 ± 24.3	127.4 ± 20.1	120.1 ± 19.1‡	110.9 ± 12.2	102.1 ± 11.5‡
Diastolic blood pressure (mmHg)	76.0 ± 6.8	76.9 ± 11.9	79.9 ± 10.6	76.7 ± 10.2‡	72.4 ± 10.5	67.2 ± 9.6‡
HDL-cholesterol (mg/dL)	33.5 ± 4.8	42.7 ± 7.9‡	36.6 ± 7.6	41.2 ± 8.8‡	37.9 ± 8.4	44.4 ± 10.1‡
Triglycerides (mg/dL)*	171.4 ± 1.5	177.5 ± 1.6	165.1 ± 1.7	164.7 ± 1.6	127.7 ± 1.7	93.4 ± 1.6‡
Fasting blood glucose (mg/dL)	122.3 ± 43.1	135.5 ± 58.9	109.1 ± 40.1	105.9 ± 37.8	89.1 ± 13.8	85.5 ± 9.1‡
Metabolic syndrome (%)	9(60)	45(73.8)	445(76.6)	476(78.4)	369(36.6)	104(12.9)‡
Abdominal obesity (%)	8(53.3)	34(55.7)	385(66.3)	380(62.6)	356(35.3)	64(8)‡
Low HDL-cholesterol (%)	10(66.7)	40(65.6)	373(64.2)	505(83.2)‡	529(52.4)	521(64.7)‡
High Triglyceride (%)	10(66.7)	49(80.3)	515(88.6)	587(96.7)‡	834(82.7)	729(90.6)‡
Hyperglycemia (%)	7(46.7)	34(55.7)	212(36.5)	238(39.2)	76(7.5)	44(5.5)‡
Hypertension (%)	5(33.3)	27(44.3)	259(44.6)	223(36.7)‡	126(12.5)	33(4.1)‡

* Log transformation; †Mean ± SD; ‡$P < 0.05$; grandfathers vs. grandmothers, fathers vs. mothers, and sons vs. daughters.

Definition of the metabolic syndrome and lipid profiles

We determined MetS status in the adult population using criteria defined by the Joint Interim Statement (JIS),[15] with modification of criteria for WC (WC ≥95 cm for both genders), based on the Guidelines of the Iranian National Committee for Obesity.[16] A participant with three of the following five criteria was defined as having the MetS: (1) TG ≥150 mg/dL or treated hyperlipidemia, (2) HDL-C<40 mg/dL in men and <50 mg/dL in women or treated dyslipidemia, (3) Blood pressure (BP) ≥130/85 mmHg or treated hypertension, (4) Fasting blood sugar (FBS) ≥100 mg/dL or treated hyperglycemia, and (5) WC ≥95 cm for both genders. For children under 18 years, MetS was defined according to Cooks guidelines,[17] which defines the MetS as having three or more of the following: (1) TG ≥110 mg/dL; (2) HDL-C ≤40 mg/dL; (3) WC ≥90th for age and sex specified according to the national reference curve[18]; (4) SBP and/or DBP ≥90th for sex, age, and height from National reference cut off points,[19] and (5) FBS ≥100 mg/dL according to the recent recommendations of American Diabetes Association.[20]

Statistical analysis

The Kolmogorov-Smirnov goodness-of-fit test was used to assess normal distribution of continuous data. All continuous data are expressed as means ± SD and categorical variables are expressed as percentage. Natural logarithm transformation was performed to normalize the distribution of TG.

Age and sex adjusted Pearson correlation coefficients were calculated among MetS and quantitative lipid components. We used exploratory factor analysis to reduce the dimension of MetS and quantitative lipid traits. The principal component method with a varimax rotation was used and the final factors were determined by eigenvalues greater than 1.0. Adjusted factor loading and explained variance of various quantitative traits were obtained. All statistical analyses were performed on SPSS software (version 15.0; SPSS, Chicago, IL, USA). Probability values <0.05 were considered statistically significant.

Familial intra-trait correlation coefficients (ICC) of MetS and quantitative lipid traits between spouses, parent-offspring, siblings, and grandparent-grandchildren were estimated using the FCOR program in Statistical Analysis for Genetic Epidemiology (v6.1.0; S.A.G.E).[21] We tabulated the affected sibling members by family size, stratifying by proband MetS status, and estimated the sibling recurrence risks by the odds ratio of proband status for MetS. Finally, multiple logistic regression was used to estimate the adjusted odds ratio and 95% confidence intervals of proband MetS status and four factors by the generalized estimating equation (GEE) model to adjust the intra-familial dependence.[22] Statistical analyses were performed on SPSS software (version 15.0; SPSS, Chicago, IL, USA).

Results

The basic characteristics of the grandparents, parents and their children are presented in Table 1. Fathers and sons were older than mothers and daughters, respectively. Grandmothers had the highest TC, LDL-C, SBP, TG, and FBS. Means of TC, LDL-C, and BMI were higher in mothers compared to fathers; in contrast, fathers had higher WC, SBP, DBP, and lower HDL-C than mothers. Also, sons had higher WC, BMI, SBP, DBP, TG, and FBS and lower HDL-C than daughters.

The highest and lowest prevalence rates of MetS were 78.4% and 60% for mothers and grandfathers, respectively; compared to sons (36.6%), daughters had lower prevalence of MetS (12.9%). Low HDL-C level and high TG were more prevalent in mothers than fathers; conversely, fathers had higher BP. Moreover, the prevalence of MetS and its components was higher in sons than in daughters.

Table 2. Family intra-trait correlations (r), equal weight to pedigree of metabolic syndrome and its components in the study population.

Variables	Spouse (266)*	Parents/offspring (1403)	Siblings (654)	Grandparents/grandchildren (162)
Total cholesterol	0.06	0.30†	0.33†	0.22†
LDL-cholesterol	0.03	0.30†	0.31†	0.20†
Waist circumference	0.11†	0.22†	0.25†	0.10
Body mass index	0.06	0.18†	0.31†	0.04
Systolic blood pressure	0.22†	0.21†	0.30†	0.09
Diastolic blood pressure	0.04	0.16†	0.31†	0.04
HDL-cholesterol	0.10†	0.16†	0.24†	0.27†
Triglyceride ‡	-0.03	0.19†	0.15†	0.20†
Fasting blood glucose	0.07	0.02	0.19†	0.10
Factor 1: Cholesterol	0.009	0.25†	0.33†	0.12
Factor 2: Obesity	0.12†	0.07†	0.25†	0.03
Factor 3: Blood pressure	0.01	0.11†	0.40†	0.09
Factor 4: Dyslipidemia/hyperglycemia	0.09	0.19†	0.19†	0.28†

*Pair numbers; †$P < 0.05$; ‡Log transformation

Table 3. Sibling recurrence risk ratios of metabolic syndrome status, specified by proband's status of the metabolic syndrome, in the study population (estimated odds ratio: 5.61, 95% confidence interval: 3.15–9.97, $P < 0.001$).

Family size	Affected sibling numbers							Total siblings
	0	1	2	3	4	5		
Proband metabolic syndrome status (+) N = 145								
1	—	—						
2	0	51	22					73
3	0	23	16	4				43
4	0	7	9	1	0			17
5	0	4	6	1	1	0		12
Total siblings	0	85	53	6	1	0		145
Family size	**Affected sibling numbers**							**Total siblings**
	0	**1**	**2**	**3**	**4**	**5**	**6**	
Proband metabolic syndrome status (-) N = 371								
1	—	—						
2	108	73	0					181
3	39	75	10	0				124
4	10	18	4	1	0			33
5	7	14	5	1	0	0		27
6	2	0	1	3	0	0	0	6
Total siblings	166	180	20	5	0	0	0	371

To determine the contribution combined traits for MetS, we calculated Pearson partial correlation between MetS components and lipid related factors of individuals, adjusted for age and gender (data not shown). As expected, the highest correlation was between LDL-C and TC (r = 0.925), while FBS and WC demonstrated the lowest correlation (r = 0.041).

The factors and patterns of factor loadings were obtained in this study (data not shown). Four factors were extracted from six continuous traits of the MetS and lipid-related variables. Factor I, which explained 22.7% of the total variance in data set, was dominated by TC and LDL-C; factor II by WC and BMI accounted for 21.8% of total variance in data set; factor III, dominated by SBP and DBP, explained 17.7% of variance, and factor IV, by HDL-C, TG, and FBS, accounted for 15.4% of total variance.

The intra-trait familial correlation of the components of the MetS and other metabolic variables, adjusted for age and sex between spouses, parent-offspring and siblings, and grandparent-grandchildren, are presented in Table 2. Sibling correlations were higher than the parent-offspring correlation, and both were much higher than those between spouses and grandparent-grandchildren, indicating the high genetic components of these quantitative components. The highest correlation was seen in factor III (BP) (r = 0.40), followed by TC and factor I (TC and LDL-C) (r = 0.33), and lastly in LDL-C, BMI, and DBP in siblings (r = 0.31). The correlation coefficients were mostly >0.2 between sibling and parent-offspring, while only the spouse SBP correlation was >0.2, representative of assertive matching in SBP.

In assessing the familial aggregation of a disease or physiological trait, the sibling recurrence risk ratio is a commonly used index.[23] Contingency tables of MetS status in affected siblings specified by their numbers are shown in Table 3. The results indicate a significant familial aggregation of MetS status among siblings and relatives; higher MetS prevalence rates were found among proband's MetS status. The patterns among relatives were similar to those of siblings. The recurrence risk ratio among siblings was 5.61 (95% confidence interval (CI): 3.15–9.97). The GEE model for predicting odds ratio for MetS status among family relatives are presented in Table 4. After adjusting for age, gender and smoking, the odds ratio of proband's MetS status decreased to 1.33 (95% CI: 1.06–1.67, $P = 0.014$). The adjusted odds ratios

Table 4. Adjusted odds ratio and 95% confidence intervals for predicting the metabolic syndrome status among family relatives.

Variables	Odds ratio	Lower 95% CI	Upper 95% CI	*P*-value
Age (year)	1.09	1.08	1.10	<0.001
Proband metabolic syndrome: yes vs. no	1.33	1.06	1.67	0.014
Females vs. males	2.35	1.94	2.83	<0.001
Smoke status: yes vs. no	0.98	0.61	1.56	0.920
Factor 1: Cholesterol	1.23	1.06	1.42	0.006
Factor 2: Obesity	7.50	5.91	9.52	<0.001
Factor 3: Blood pressure	4.20	3.51	5.02	<0.001
Factor 4: Dyslipidemia/hyperglycemia	4.86	4.03	5.87	<0.001

of principal factors I (cholesterol), II (obesity), III (BP), and IV (dyslipidemia/hyperglycemia) for predicting MetS were significant, with the highest odds ratio observed for factor II (obesity), 7.50 (95% CI: 5.91–9.52), followed by factor IV (dyslipidemia/hyperglycemia), 4.86 (95% CI: 4.03–5.87); the odds ratio of factor III (BP), 4.20 (95% CI: 3.51–5.02), and lastly for factor I (cholesterol), 1.23 (95% CI: 1.06–1.42), all of which were significant.

Discussion

The current study used a genetic epidemiologic approach to investigate the effects of genetic components on the recurrence risk ratio of cardio-metabolic risk factors in a Tehrani population. We demonstrated significant familial correlations, which the recurrence risk ratio of MetS being over five-fold among family members. The study results strongly suggest the genetic susceptibility to MetS, and the obesity factor was found to predict MetS most significantly in this population.

In the current study, we clearly quantified the effects of genetic factors on MetS, its components, and lipid-related factors. Most previous studies included various definitions for MetS defined variables for factor analysis and yielded fewer or more factors compared to our study.[24,25] We specified four independent factors to prevent multi-collinearity problems for statistical inference.

Intra class correlation coefficient is commonly used to assess familial aggregation; when families have different numbers of offsprings, different ICC estimators can be obtained depending on the weight scheme for the contribution of a family. Previous studies on MetS have shown significant familial correlation among different subjects.[11,26] The ICC obtained from our study are comparable to those reported in the literature, such as an ICC of 0.20–0.34 for BMI and WC, 0.15–0.31 for TG and HDL-C, 0.17–0.39 for BP, and 0.20–0.32 for TC and LDL-C[26–28]; the ICC of FBS in our study is close to that from a Chinese study, which reported an ICC of 0.18–0.20 among men and women,[28] and can be explained by the high rates of consanguineous marriages in the Iranian population, in which genetic factors play a key role.[29,30]

In addition, we specified binary and continuous traits of MetS, and estimated recurrence risk ratios among siblings. Sibling recurrence risk ratio can provide good hints for genetic components.[22] In the current study, the significant siblings recurrence risk ratio and the results imply that genetic components strongly existed among Tehrani population; both genetic and shared environmental factors contribute to the aggregation of MetS and its components among siblings, as documented by some previous twin studies, which demonstrated that both play an important role in the etiology of the MetS.[11,31]

Finally, we incorporated statistical methods such as GEE to tackle the dependence among family members. Due to the clustering of multiple risk factors, MetS is a difficult phenotype in terms of identifying underlying genetic factors. Our results are consistent with other studies and lend support to the opinion of other researchers.[26] Furthermore, obesity factor is viewed as a central factor for the MetS, especially since urbanization and globalization have accelerated the obesity endemic in non-Western countries.[32] Our study also demonstrated a high prevalence of central obesity among Tehrani adolescents and their families. Weight control should be given top priority for MetS prevention programs in areas of rapid economic progress. Family-based lifestyle interventions on body weight control and physical activity would be useful in community populations.

Our study has some limitations. First, the response rates of the parents and grandparents were 60% and 54%, respectively, and up to a quarter of the grandparents and parents' data were missed in the study, yielding a low sample size for grandparents; this could also reduce the power for estimating spouse and grandparent/grandchildren correlations. Second, family size was not adjusted for in this study. Third, we did not take into account the diet, level of physical activity or socio-economic status, and information of puberty; only smoking was considered. Finally, we cannot differentiate common environmental from pure genetic factors in this study. However, this study, to the best of our knowledge, is the first report to use a genetic epidemiology approach to address the genetic components and recurrence risk ratio of cardio metabolic risk factors in an Iranian population.

Conclusion

In conclusion, we clearly demonstrated familial aggregation and recurrence risk ratio of the MetS and lipid components among a Tehrani population of Iran. The results showed a high five-fold risk of the MetS in sibling with MetS proband. Moreover, findings confirm the importance of obesity factor for the aggregation of the MetS, which was almost seven-fold in this population.

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