Genetics of metabolic syndrome and related traits

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Chapter 2

Prevalence and heritability of the metabolic syndrome and its individual components in a Dutch isolate: The Erasmus Rucphen Family (ERF) study

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ABSTRACT

Background: Metabolic syndrome (MetS) is defined by a combination of abnormalities that are all individual risk factors for the development of type 2 diabetes and/or cardiovascular disease. The etiology of MetS includes both an environmental and genetic component. We studied prevalence and heritability of MetS and its individual components in a Dutch genetic isolate.

Methods: The Erasmus Rucphen Family study (ERF) consists of some 3000 genealogically documented individuals from a Dutch genetic isolate. Data on waist circumference (WC), blood pressure (BP), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fasting plasma glucose values (FPG) are available. MetS was defined according to the International Diabetes Federation (IDF) (2003) and National Cholesterol Education program Adult Panel III (NCEP ATPIII) criteria. Variance component analysis was applied to extended family data to test for evidence of heritability.

Results: The prevalence of MetS in the ERF cohort ranged from 23-37% depending on MetS definition and gender considered. Low HDL-C and high WC are the main contributors to MetS. The heritability of MetS corrected for sibship effect was 10.6% (P = 0.01) according to IDF and 13.2% (P = 0.07) according to NCEP ATPIII criteria. In addition, the heritability of individual components of MetS were analyzed and found to range from 21.9 to 42.9%. The highest heritability was found for HDL-C (42.9%, $P < 0.0001$) and WC (37.8%, $P < 0.0001$). In addition, WC, SBP, HDL-C and TG, showed low to moderate genetic correlation (RhoG) between genders, whereas FPG and DBP showed absolute genetic correlation between genders.

Conclusion: Although the prevalence of MetS was high, the heritability of MetS in the ERF population was found to be moderate. The high heritability of the individual components of MetS indicates that the genetic dissection of MetS should be approached from its individual components.

INTRODUCTION

In populations that have adopted the Western life style, risk factors for type 2 diabetes (T2D) and cardiovascular disease (CVD) are strongly increased. These include high blood pressure (BP), low plasma high density lipoprotein cholesterol (HDL-C), elevated values of plasma triglyceride (TG), increased waist/hip ratio (WHR) or body mass index (BMI) and elevated levels of fasting plasma glucose (FPG). The combined presence of several of these risk factors has been termed the Metabolic Syndrome (MetS) or Syndrome X. Several definitions of MetS have been formulated over the years[1,2].

MetS as entity has proven to help clinicians in risk estimation for CVD and T2D. The question we raise in the present study is whether this entity is also of use in genetic research. Clustering of obesity and other cardiovascular risk factors might be explained by a common genetic origin, thus combining factors into a single outcome, as defined by MetS, may improve the power of gene discovery. However, recently the interest in defining gene specific endo-phenotypes in genetic research, in which syndromes are decomposed in traits with a homogeneous genetic origin, has increased. This approach does not favor gene discovery in MetS as entity, but favors studies of individual components. As the heritability of a trait is one of the main determinants of the power of gene finding, we compared this parameter in MetS and its individual components.

In the present study, we determined the prevalence of MetS and estimated the heritability of MetS and its individual components (by means of a general polygenic model, a polygenic household model

and polygenic gender model, respectively) in a Dutch genetically isolated population with extensive phenotypic and genealogical information. As in all isolated populations, our isolate is characterized by genetic drift and founder effect[3]. Genetic drift reduces the genetic variation. In recent simulation studies of genetic isolation, it was shown that rare variants may disappear completely or become common but it is unlikely that common alleles disappear[4]. Thus, genetically isolated populations will provide insight in both common and rare genetic variants that predispose to common complex diseases such as the metabolic syndrome[5,6].

SUBJECTS AND METHODS

In the present study, we used data of the Erasmus Rucphen Family study (ERF) which is embedded in a rural isolated population (Genetic Research in Isolated Populations; GRIP). This young, genetic isolate in the southwest of the Netherlands was founded in the mid-eighteenth century. Minimal immigration and/or marriages occurred between surrounding settlements due to social and religious reasons. This population experienced a fast expansion, at the moment this region counts roughly 20.000 inhabitants. The ERF population includes 3,000 individuals, who were not selected based on health information, but rather comprises of living descendants of 22 couples with at least 6 children baptized in the community church around 1850-1900 (approximately a total of 150 founders). Details about the genealogy of the population are described elsewhere[6,4,3]. The study protocol was approved by the medical ethics board of the Erasmus MC Rotterdam, the Netherlands. All investigations were carried out in accordance with the Declaration of Helsinki.

Plasma concentrations of triglyceride (TG), high density lipoprotein – cholesterol (HDL-C), fasting plasma glucose (FPG), diastolic and systolic blood pressure (DBP and SBP), waist circumference (WC), anti-diabetic (insulin, oral hypoglycemic) treatment, antihypertensive treatment and lipid lowering agents were determined as described previously[5,6,7].

We applied two different MetS definitions (table 1) in our study, namely the definition formulated by the National Cholesterol Education program Adult Panel III (NCEP ATPIII) and the definition formulated by the International Diabetes Federation (IDF).

Spss 11.0.1 (SPSS, Chicago, IL, USA) was used for selection, descriptive and regression analysis. For the prevalence of MetS according to the IDF definition, the Caucasian WC threshold values of >94 cm for males and >80 cm for females were used[8]. Correlations between components were based on transformed data. Pearson correlation coefficients were used to examine the association of MetS components and age, to confirm the presence of important cluster of traits within the MetS. Gender differences were evaluated by means of the Chi squared algorithm or Student's T-test. Heritability estimates were calculated using the SOLAR software version 2.05 (http://www.sfbr.org/solar/4.0.7.doc/00.contents.html). The individual components, WC, HDL-C, S/DBP, and TG showed a small deviation from a normal distribution within the ERF population, of which the software is extremely sensitive. Therefore heritability estimates of these components were based on the log normal transformed values. SOLAR's tdist function was used when traits remained to show some kurtosis. Where necessary, traits were multiplied with a factor (suggested by the software) for an optimal trait standard deviation.

The polygenic model was applied for all traits (MetS as binary trait, individual components as quantitative traits) which is assuming that an infinite number of genetic factors with a small additive effect contribute to the trait variance. In family based heritability estimations, the shared environment

within one household and shared genetic dominant effect between sibs within one household, may inflate the outcome of the heritability estimate. Therefore we corrected our heritability estimations for sibship effect (s). This shipship effect is an estimate of phenotypic similarity, induced by the progeny of the same parents. Thus, the sibship effect is a combination of effects induced by sharing early childhood environment and dominant genetic variation. Detailed description of calculation of heritability estimates was described by others[4,6]. To estimate the effect of gender specific heritability and the genetic correlation of a trait between genders (RhoG), bivariate polygenic analysis (trait + gender, covariates: age and inbreeding coefficient) was applied on all individual traits of the MetS[9,10].

RESULTS

Threshold values for MetS definitions according to the IDF and the NCEP ATPIII are given in table 1. Values for WC; HDL-C; TG; FPG; DBP and SBP were available for 2860 individuals. Table 2 shows the mean demographic characteristics of the study population. The mean age of the 1286 males was 49.4 years old (range 17.6 to 86.5) and the mean age of the 1574 females was 48.3 years old (range from 16.7 to 86.1).

Table 1: Metabolic syndrome definitions

	IDF (2003)[a]	ATPIII (2001)
male waist circumference (cm)	≥ 94	>102
female waist circumference (cm)	≥ 80	> 88
Fasting plasma glucose (mmol/L)	≥ 5.6 [b,c]	≥ 6.1
Systolic blood pressure (mm Hg)	≥ 130 [c]	≥ 135 [c]
Diastolic blood pressure (mm Hg)	≥ 85 [c]	≥ 85 [c]
male HDL-cholesterol (mmol/L)	< 1.03 [c]	< 1.0
female HDL-cholesterol (mmol/L)	< 1.29 [c]	< 1.3
Triglycerides (mmol/L)	≥ 1.7 [c]	≥ 1.7

a Europids

b included previously diagnosed type 2 diabetes patients

c included treatment patients.

The prevalence of MetS was 36.8% in males and 31.0% (P = 0.01) in females according to the IDF MetS definition and 26.7% in males and 22.8% (P = 0.02) in females according to the NECP ATPIII definition. As expected, the prevalence of MetS strongly correlated with age. We divided the population in six age groups: younger than 30 years old (N=294), 30-40 years old (N= 534), 40-50 years old (N=657), 50-60 years old (N=686), 60-70 years old (N=505) and 70 years old or older (N=184). Figure 1a illustrates the gender specific percentages within each age group of the prevalence of MetS according to the IDF definition. Figure 1b represents the same graph for the NCEP ATPIII definition. Using the IDF definition, in the group of 30-40 years old and using the NCEP ATPIII definition, in the groups of 30-40 and 40-50 years old the prevalence of MetS was significant higher in males compared to females.

According to the IDF definition of MetS, WC plus a minimum of any two other components are necessary for the expression of MetS. In contrast, the NCEP ATPIII definition does not require WC as an essential component for MetS expression. In this study, we investigated which combination of components contributed most to both the prevalence of the IDF MetS and NCEP ATPIII MetS. Table 3 represents all possible combinations of components in both genders, which can contribute to the expression of MetS. In these calculations, the blood pressure component was combined (BP =

Table 2: Demographic characteristics of the ERF population

Trait	Mean ± SE total	Mean ± SE males	females	Mean ± SE	*P*-value [a]
N	2860	1286		1574	
Medication lipids	366(12.8)	193(15.0)		173(11.0)	< 0.01
Medication DM	137(4.8)	74(5.8)		63(4.0)	< 0.05
Medication hypertension	492(17.2)	241(18.7)		251(15.9)	< 0.05
Age (years)	48.8 ± 0.27	49.4 ± 0.40		48.3 ± 0.36	< 0.05
Waist circumference (cm)	87.7 ± 0.25	94.2 ± 0.33		82.3 ± 0.32	< 0.001
Fasting plasma glucose (mmol/L)	4.7 ± 0.21	4.84 ± 0.034		4.51 ± 0.026	< 0.001
Systolic blood pressure (mm Hg)	140.1 ± 0.38	143.6 ± 0.512		137.2 ± 0.538	< 0.001
Diastolic blood pressure (mm Hg)	80.4 ± 0.19	82.05 ± 0.276		79.0 ± 0.248	< 0.001
HDL-cholesterol (mmol/L)	1.3 ± 0.007	1.13 ± 0.009		1.40 ± 0.009	< 0.001
Triglycerides (mmol/L)	1.3 ± 0.146	1.49 ± 0.025		1.23 ± 0.016	< 0.001

a Difference between genders, *P* value by t-test. Value presented as N (%) or mean ± standard error.

SBP and/or DBP). For calculation within the IDF MetS, in total 11 combinations are possible with the components WC, HDL-C, TG, FPG and BP. Six of these combinations consisted of three components (for example WC + HDL-C + TG), four consisted of four components and one contribution included all components. For calculation within the NCEP ATPIII MetS in total 16 combinations are possible with the components WC, HDL-C, TG, FPG and BP. Ten of these combinations consisted of three components, five consisted of four components and one combination included all components. To determine the most prevalent contributions of combinations of the traits to MetS according to both definitions in the ERF population, we calculated Pearson correlations for all MetS components and age. These data are presented in table 4. Three main clusters of components contributing to MetS can be observed (bold in table 3). For males, these clusters are the same for the two definitions, [WC / HDL-C / BP] and [WC / HDL-C / TG / BP]. For females differences in composition of these clusters was observed between both definitions. The main female clusters according the IDF definition are [WC / HDL-C / BP] and [WC / HDL-C / TG / BP], but for the NCEP ATPIII definition [HDL-C / TG / BP] and [WC / HDL-C / TG / BP] contribute the most to the prevalence of MetS. Significant correlations between individual components (bilateral) were more prevalent in females than in males (table 4).

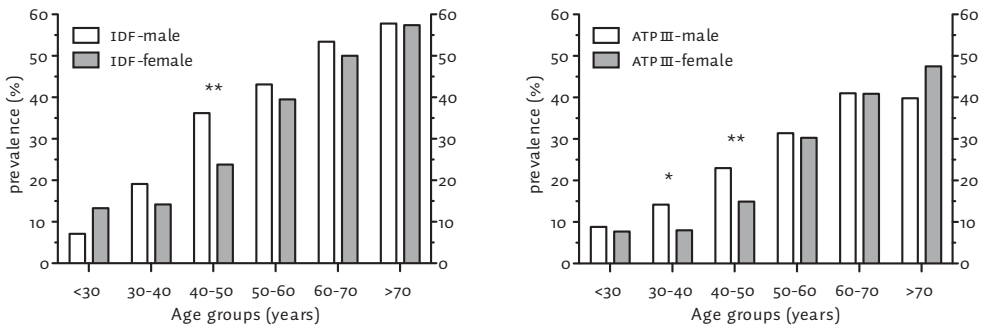

*Figure 1 Prevalence (%) of the metabolic syndrome (MetS) in age groups <30 years, 30–40, 40–50, 50–60, 60–70, and >70 years in the MetS subgroup of the Erasmus Rucphen Family population according to two different MetS definitions. Panel A: International Diabetes Federation (IDF). Panel B: US National Cholesterol Education Program Adult Panel III (NCEP ATPIII). *P<0.05; **P<0.001.*

WC in females correlates with all other components. HDL-C and TG are correlated in both genders. The BP components showed a somewhat lower correlation with WC and no correlation with HDL-C in females.

Table 3: Contribution (%) of possible combinations of individual components to MetS expression (both IDF MetS and NCEP ATPIII MetS).

Parameter combination	IDF MetS (%)		NCEP ATPIII MetS (%)	
	male [a]	female [b]	male [c]	female [d]
1 WC / HDL-C / TG	3.6	4.7	4.7	5.2
2 WC / HDL-C / FPG	0.6	0.2	0.6	0.3
3 WC / TG / FPG	0.2	0.0	0.0	0.0
4 WC / TG / BP	10.3	5.9	4.7	7.6
5 WC / HDL-C / BP	**27.3**	**40.8**	**31.5**	14.0
6 WC / FPG / BP	3.8	3.1	1.9	1.7
7 HDL-C / FPG / BP	-	-	2.2	3.8
8 HDL-C / TG / BP	-	-	11.7	**24.5**
9 HDL-C / TG / FPG	-	-	0.0	0.3
10 TG / FPG / BP	-	-	0.0	2.3
11 WC / TG / FPG / BP 4.7	1.0	0.8	2.6	
12 WC / HDL-C / FPG / BP	0.0	0.0	6.1	5.2
13 WC / HDL-C / TG / BP	**26.4**	**22.3**	**25.9**	**22.2**
14 WC / HDL-C / TG / FPG	11.8	10.9	0.0	0.9
15 HDL-C / TG / FPG / BP	-	-	2.8	3.2
16 WC / HDL-C / TG / FPG / BP	11.4	11.1	7.0	6.1

WC, waist circumference; HDLC, high density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose; BP, blood pressure; IDF, International Diabetes Federation; NECP ATPIII, National Cholesterol Education program Adult Panel III.
- , combination not represented by definition.

For both MetS definitions, we estimated the heritability in the ERF population (N=2488). Furthermore, we estimated the contribution of the sibship effect (early childhood environmental factors and genetic dominant effects) for both definitions. Table 5 illustrates the heritability estimates without consideration of the sibship effect (s) and table 6 illustrates the heritability estimates with consideration of the sibship effect. For both estimations, with and without sibship effect (s), the covariates we included were: gender, age and inbreeding coefficient. The heritability of the IDF-defined MetS, even when corrected for sibship effect, still reached significance ($P = 0.01$) whereas the heritability of the NCEP ATPIII-defined MetS was not but borderline significant ($P = 0.07$). In addition to the heritability of MetS definitions, we also estimated the heritability of the individual components of MetS in the ERF population (N=2488). SOLAR's analysis of covariance is not sensitive for altered trait values due to (limited) medication use (data not shown). Because all traits showed some skewness or extra kurtosis, these heritability estimates were based on natural log transformed data (table 5) and were necessary, t-distribution modeling was applied. In addition, we estimated the contribution of the sibship effect to the heritability of each component (table 6). This sibship effect inflated the heritability of all traits, with exception of HDL-C.

Table 4: Pearson correlation coefficients all components in ERF MetS (IDF) subjects

male n =473 [a]	Age	HDL-C	WC	TG	FPG	SBP		
		SBP	FPG	TG	WC	HDL-C	Age	**female n =488** [a]
HDL-C	0.09	0.40 **	0.06	-0.04	0.16 **	-0.01	-0.05	*DBP*
WC	0.03	-0.08	0.22**	0.04	0.12 **	0.06	0.50 **	*SBP*
TG	-0.16**	-0.11**	0.06	0.16**	0.29 **	-0.00	0.20 **	*FPG*
FPG	0.19**	0.03	0.13**	0.02	0.15 **	-0.12 **	0.10 *	*TG*
SBP	0.30**	0.15 **	0.07	-0.03	0.17 **	-0.16 **	0.04	*WC*
DBP	0.01	0.13 **	0.10*	0.16**	0.04	0.10 *	0.18 **	*HDL-C*

HDL-C, high density lipoprotein cholesterol; WC, waist circumference; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; IDF, International Diabetes Federation. a Above diagonal (in italics) represents female correlation values.
*P<0.05, **P<0.01.

Table 7 represents gender specific heritability estimates and the genetic correlation of a trait between genders (RhoG), for all individual MetS traits. Inclusion of the sibship effect in this model was not appropriate (overmodelling). The lowest significant genetic correlation between genders (RhoG) was observed for WC and SBP (RhoG WC = 69.9 ± 14.0%, RhoG SBP = 61.5 ± 19.4%), whereas absolute genetic correlation between genders was observed for FPG and DBP (both RhoG = 100.0%). Both lipid traits, HDL-C and TG, showed moderate genetic correlation between genders (RhoG – HDL-C = 82.5 ± 12.6%, RhoG – TG = 85.5 ±17.5%)

Table 5: Heritability of IDF and NCEP ATPIII MetS definitions and its natural log transformed individual components in ERF population.

Parameter	**h2 (%)**[a]	**SEM**	***P*-value**[b]
n	**2488**		
IDF	14.3	4.8	$<10^{-06}$
ATPIII	19.2	5.6	$<10^{-06}$
ln WC	40.5	4.2	$<10^{-06}$
ln FPG	28.2	4.0	$<10^{-06}$
ln SBP	27.9	3.9	$<10^{-06}$
ln DBP	27.0	3.9	$<10^{-06}$
ln HDL-C	42.9	4.1	$<10^{-06}$
ln TG	30.8	3.9	$<10^{-06}$

IDF, International Diabetes Federation; NCEP ATPIII, National Cholesterol Education program Adult Panel III; WC, waist circumference; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol TG, triglyceride. a Heritability based on polygenic model without consideration of the sibship effect (s), covariates: gender, age and inbreeding coefficient
b *P* values were derived using the likelihood ratio test.
*P<0.05, **P<0.01.

DISCUSSION

The prevalence of MetS in this Dutch genetic isolate according the IDF definition is 36.8% in males and 31.0% (P < 0.01) in females. According to the NECP ATPIII definition the prevalence of MetS was 26.7% in males and 22.8% (P < 0.02) in females. The two most important clusters of individual components, contributing to the manifestation of MetS (in both genders and both definitions) were [WC / HDL-C / BP] and [WC / HDL-C / TG / BP]. Another important cluster according the NECP ATPIII definition, in females was [HDL-C / TG / BP]. The heritability of MetS in our genetically isolated population was 10.6% ± 5.3% according to the IDF definition (p=0.07) and 13.2% ± 6.0% according to the NECP ATPIII definition (p<0.05). The heritability of the individual components ranged from 21.9% (DBP) to 42.9% (HDL-C). Low significant genetic correlations between genders were

Table 6: Heritability of IDF and ATP MetS definitions and its log normal transformed individual components in ERF population.

Parameter	h2 (%)[a]	SE	P-value[b]	s (%)[c]	SE	P-value[b]
n	2488					
IDF	10.6	5.3	< 0.05	9.05	6.2	0.07
ATPIII	13.2	6.0	0.07	15.89	7.4	< 0.05
ln WC	37.8	4.6	$<10^{-06}$	5.6	3.4	< 0.05
ln FPG	22.7	4.7	$<10^{-06}$	9.6	3.6	< 0.01
ln SBP	25.4	4.3	$<10^{-06}$	7.8	3.3	< 0.01
ln DBP	21.9	4.6	$<10^{-06}$	2.7	3.3	0.20
ln HDL-C	42.9	4.1	$<10^{-06}$	0.0	-	-
ln TG	28.3	4.4	$<10^{-06}$	4.1	3.3	0.10

IDF, International Diabetes Federation; NCEP ATPIII, National Cholesterol Education program Adult Panel III; WC, waist circumference; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol TG, triglyceride.a Heritability based on polygenic household model with consideration of the sibship effect (s), covariates: gender, age and inbreeding coefficient.
b P values were derived using the likelihood ratio test.
*P<0.05, **P<0.01.

observed for WC and SBP (RhoG: 69.9% and 61.5% respectively) Absolute genetic correlation between genders was observed for FPG and DBP (RhoG both 100.0). Moderate genetic correlation between genders, were observed for HDL-C and TG (RhoG: 82.2% and 85.5% respectively).

Although our genetically isolated population was not selected on disease phenotype, the population in general suffers from mild overweight (mean WC male = 94.2 ± 0.33 cm and mean WC female = 82.3 ± 0.32 cm) and mildly elevated blood pressures (mean SBP male = 143.6 ± 0.5 mm Hg, mean DBP male = 82.05 ± 0.3 mm Hg). It cannot be excluded that these phenotypic profiles are the consequence of enrichment of (rare) pathogenic alleles due to genetic drift associated with genetically isolated populations. Moreover, the ERF cohort is from a rural region, of which has been shown to be enriched in unfavorable metabolic profiles as compared to urban regions[11].

Relatively little information is available on the prevalence of MetS in Dutch populations. In a Dutch familial hypercholesterolemia (FH) patient population, a prevalence of 31% of MetS was found.

Table 7: Heritability of gender specific natural log transformed individual components in ERF population.

	h2 (%)[a]	SE	P [b]	h2 (%)[a]	SE	P [b]	RhoG [a]	SE	P [b]
	Female N =1397			Male N = 1091					
ln WC	53.7	6.6	$<10^{-06}$	37.6	8.2	$<10^{-05}$	69.9	14.0	0.03
ln FPG	34.4	6.5	$<10^{-06}$	25.4	6.1	$<10^{-04}$	100.0	-	-
ln SBP	42.9	6.6	$<10^{-10}$	20.3	7.5	< 0.01	61.5	19.4	0.05
ln DBP	42.6	6.7	$<10^{-09}$	14.7	4.6	< 0.01	100.0	-	-
ln HDL-C	53.0	7.1	$<10^{-13}$	42.0	7.7	$<10^{-07}$	82.2	12.6	0.16
ln TG	35.6	6.7	$<10^{-06}$	31.7	7.4	$<10^{-04}$	85.5	17.5	0.41

WC, waist circumference; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol TG, triglyceride.
a Heritability and RhoG (% shared genetics between genders) based on polymod model, RhoE (% shared environment between genders) forced to 0, covariates: age and inbreeding coefficient. b P values were derived using the X_2 test.

This study also reported, in a population suffering from CVD or other vascular disease, a prevalence of MetS ranging from 41-58%[12]. Data on two populations in the Southwest of Germany[11] showed a notably higher prevalence of MetS in rural as compared to urban populations, (urban 10%-15%, rural 20%-25%). Others[13] reported the prevalence of MetS in different ethnic groups. A Hispanic cohort (enriched for T2D) had a very high prevalence of MetS (73%). Overall, the prevalence of MetS in the Western world is estimated to vary between 10-35% (depending on age)[14,15,16]. Thus, the prevalence of MetS in the ERF population is relatively high. The higher prevalence of MetS according to the IDF definition as compared to the NCEP ATPIII definition is caused by the less stringent threshold values of the IDF definition. The significant difference in prevalence of MetS between genders is clearly a consequence of differences of prevalence in the first three age groups, < 30, 30-40 and 40-50 years old (figure 1). Women in the pre-menopausal period are apparently protected from MetS, as also reported by others[17].

In this study, we calculated the contributions to the total prevalence of MetS of all different combinations of individual components. The two most important contributors, for both genders, to the IDF MetS were [WC / HDL-C / BP] and [WC / HDL-C / TG / BP] (bold in table 3). The three most important contributions to the NCEP ATPIII MetS were [*male* WC / HDL-C / BP], [*female* HDL-C / TG / BP] and [*both genders* WC / HDL-C / TG / BP]. (bold in table 3). These findings were partly confirmed by Pearson correlation analysis of all traits, age included (table 4). In male IDF MetS subjects, a clear and significant correlation was found between HDL-C, TG and both BP components. In female IDF MetS subjects, HDL-C mainly correlated with WC and TG. The clustering of TG, HDL-C and WC is in line with previous findings[18,19,20]. The early metabolic syndrome definition was mainly determined by insulin resistance. Interestingly, FPG, is virtually absent in the most important clusters, contributing the most to MetS in our population. The result that FPG not only plays a minor role in MetS clusters, but also shows a relative moderate heritability estimate (22.7 %) in comparison with for example HDL-C, is in concert with findings of others. Apparently the environmental contribution to alterations in FPG seems to be prominent.

A heritability of 24% for MetS (NCEP ATPIII) in a Caribbean-Hispanic population has been reported by Lin *et al*[21]. Factor analysis in this study suggested two clusters of components: A lipid / obesity / plasma glucose cluster and a second blood pressure cluster. The first cluster showed the highest heritability (44%). Bayoumi *et al* reported a heritability of MetS (binary trait) in healthy Omani Arab families (N=1277) of 38%. Individual components as HDL-C and BMI showed the highest heritability in these families[22].

The heritability of MetS in our genetic isolated population was moderate (IDF = 10.6% $\pm$ 5.3%, NCEP ATPIII = 13.2% $\pm$ 6.0%) in comparison with data of others. However, our estimates of heritability of MetS were based on a complex pedigree structure, far more complex than a family pedigree. This complex pedigree structure allowed us to correct for the sibship effect, which should be a standard procedure to avoid substantial inflation of the heritability estimate due to early childhood environment (household-effect) and dominant genetic factors.

In the present study, the heritability estimations for the individual components of MetS were based on quantitative values. The heritability estimation found for individual components of MetS, ranged from 21.9% $\pm$ 4.6% for the DBP component to 42.9% $\pm$ 4.1% for the HDL-C component. Interestingly, we did not find evidence for a contribution of the sibship effect to this trait, which suggests a dominant role for strong genetic factors causing variation in plasma HDL-C values. The heritability of our MetS individual traits correspond well with findings of others in general populations (Omani Arab families)

and genetically isolated populations as the Hutterite population and Sardinian population. The Sardinian population is a large genetically isolated population which has already been useful in the identification of genes involved in several Mendelian disorders. Pilia *et al* found that, in a Sardinian cohort, the heritability of the MetS individual traits: fasted serum glucose, HDL-C, TG and WC was 31.8%, 47.1%, 29.6%, and 31.2% respectively[23]. The Hutterite population lives on nine communal farms (colonies) in South Dakota, USA and involves participants which are descendants of only 64 Hutterite ancestors who were born in the mid-eighteenth century. Abney *et al*[24] and Ober *et al*[25], both reported on the heritability in the Hutturite population. They found heritabilities of 37% for plasma TG, 45% for SBP and 21% for DBP.

Gender specific genetic architecture (heritability) of several individual MetS traits and several MetS related traits (such as plasma insulin, BMI and low density lipoprotein cholesterol, LDL-C) was reported by Weiss *et al*[9] and Pan *et al*[10] in the genetically isolated Hutterite population. The latter concluded that the individual MetS traits SBP and TG showed significant X chromosome effects, HDL-C showed a non-X chromosome gender effect and DBP showed no significant gender effects. The majority of our findings are in concert with these conclusions of Pan *et al*. Gender specific genetic architecture (genetic correlation or Rho G between genders) was found for the individual MetS traits WC, SBP, HDL-C, and TG whereas for FPG and DBP no evidence was found for differences in the genetic architecture between genders (RhoG = 100%).

Our findings suggest that genetic dissection of MetS as compound syndrome has a low power and should be approached by studying the genetics of the individual traits of MetS[21]. However, the observation that a limited set of clustered risk factors are the predominant contributors to MetS indicates that these clusters may have a common genetic origin. The power of genetic dissection using limited sets of risk factors is compromised by the limited number of subjects in the sub-selection. Alternatively, the interaction between clustered components within MetS can be studied by means of an epistasis model to study gene-gene interactions in the whole population[26].

Difference in the genetic architecture between genders is striking. Our findings and findings of others[9,10] indicate that these differences seem to be common in quantitative traits. Four of six of our MetS individual traits: WC, SBP, plasma HDL-C and plasma TG, show large to moderate differences in genetic architecture between genders. These findings indicate that analyses for novel loci should imply gender specific analysis

In conclusion, the present study on the prevalence and heritability of MetS and the individual components in a Dutch genetically isolated population provides a good basis for future genetic analyses to identify genetic risk factors for individual components contributing to MetS.

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