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Genetic variants and the metabolic syndrome: a systematic review

C. M. Povel[1,2], J. M. A. Boer[1], E. Reiling[1] and E. J. M. Feskens[2]

[1]National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands; [2]Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands

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Address for correspondence: CM Povel, RIVM, Centre for Nutrition and Health, Postbus 1, 3720 BA Bilthoven, the Netherlands. E-mail: cecile.povel@rivm.nl

Summary

Several candidate gene studies on the metabolic syndrome (MetS) have been conducted. However, for most single nucleotide polymorphisms (SNPs) no systematic review on their association with MetS exists. A systematic electronic literature search was conducted until the 2nd of June 2010, using HuGE Navigator. English language articles were selected. Only genes of which at least one SNP–MetS association was studied in an accumulative total population ≥4000 subjects were included. Meta-analyses were conducted on SNPs with three or more studies available in a generally healthy population. In total 88 studies on 25 genes were reviewed. Additionally, for nine SNPs in seven genes (*GNB3*, *PPARG*, *TCF7L2*, *APOA5*, *APOC3*, *APOE*, *CETP*) a meta-analysis was conducted. The minor allele of rs9939609 (*FTO*), rs7903146 (*TCF7L2*), *C56G* (*APOA5*), *T1131C* (*APOA5*), *C482T* (*APOC3*), *C455T* (*APOC3*) and *174G>C* (*IL6*) were more prevalent in subjects with MetS, whereas the minor allele of Taq-1B *(CETP)* was less prevalent in subjects with the MetS. After having systematically reviewed the most studied SNP–MetS associations, we found evidence for an association with the MetS for eight SNPs, mostly located in genes involved in lipid metabolism.

Keywords: Metabolic syndrome, SNPs, systematic review.

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Introduction

The metabolic syndrome (MetS) is a common multicomponent condition including abdominal obesity, dyslipidaemia, hypertension and hyperglycaemia. It is associated with an increased risk of coronary heart disease (CHD) and type 2 diabetes (T2D). The prevalence of MetS, which is currently around 30%, is rising worldwide (1).

Heritability estimates for MetS range from 10% to 30% (2–4), indicating that MetS is partly heritable. Knowledge of the exact genetic factors underlying MetS development may help to explain why the features of MetS frequently co-occur within one individual. In order to detect genes underlying MetS development several candidate gene studies have been performed with inconsistent results. However, no systematic review has been conducted to date, and thus no clear overview of the available evidence on the genetics of the MetS exists. Therefore, the objective of this paper is to systematically review the studies on single nucleotide polymorphisms (SNPs) and MetS, and where possible to summarize the results using meta-analyses.

Methods

Search strategy

An electronic literature search was conducted using HuGE Navigator. HuGE Navigator is a database of published population-based epidemiologic studies of human genes extracted and curated from PubMed since 2001 (5).

Previous validations on selected gene-disease associations showed that HuGE Navigator was equally sensitive, but more specific than PubMed (6).

For the Huge Navigator search, the search term 'metabolic syndrome × [Text MesH]' was used. This search retrieved articles on the association between MetS and any genetic variant. The latest search was undertaken on 2nd of June 2010. As HuGE Navigator only retrieves articles published since 2001, an additional PubMed search was done. For the PubMed search, the search term 'metabolic syndrome × [Text + MesH] with limits on publication date from 1990/1/1 to 2001/12/31' was used.

Eligibility criteria

Articles were included when they contained MetS as outcome and were: published in English; original research articles; conducted in humans; and testing for SNP main effects. All existing definitions of MetS (Table S1) were eligible as study outcome.

Genes were included if two or more articles were retrieved on the same gene, and at least for one of the SNPs in this gene the accumulative total study population was ≥4000 subjects. A study with 4000 subjects has a power of 80% to detect an OR ≤0.8 or an OR ≥1.2, assuming a significance level of 0.05, a MetS prevalence of 30% and a minor allele frequency (MAF) of 0.25. An exception was made for the *ADIPOQ* gene, which has been related to MetS in linkage studies (7). The *ADIPOQ G276T* (rs1501299) polymorphism was studied in an accumulative total population of 3865 subjects only. However, because the MAF of this SNP was 0.30 instead of 0.25, the power to detect an association was 90%. For other SNPs investigated in 3000–3999 subjects either the MAF was too low to obtain sufficient power, or the prior evidence substantiating an association with MetS was weak.

Included studies were eligible for inclusion in the meta-analyses if they had a cross-sectional or case–control design, and if the crude genotype distribution according to MetS status was available. If the genotype distribution could not be extracted from the original research article, investigators were contacted via email. Meta-analyses were carried out for SNPs with both three or more eligible studies available in a generally healthy population and with inconsistent study outcomes.

Data extraction

Data extraction was conducted by one author (CMP). For quality control, data were extracted by two of the other authors (JMAB, ER) for 10% of the entered papers. Only minor discrepancies were found. For each article the following information was extracted: authors, publication year, sample size, number of MetS cases, ethnicity, health status of the population (e.g. CHD or T2D patients), study design, mean age, percentage men, crude genotype distribution by MetS status, odds ratio and the reported measure of variance. For the selected genes all SNP–MetS associations published, independent of sample size, were extracted. If results were given for multiple MetS definitions, results for the definition of the NCEP ATPIII, which is the most common definition, were extracted. If results were presented separately for men and women an aggregate effect measure was calculated where possible.

Data analyses

For SNPs located in the same gene we checked the correlation coefficients according to HapMap. If SNPs had a correlation ≥0.8 we mentioned this in the results.

For SNPs included in the meta-analyses, ORs of individual studies were recalculated from the available genotype distributions according to an allelic model. Afterwards, combined ORs were calculated using random effect models and forest plots were drawn. Heterogeneity was investigated by the I^2 statistic. Roughly, I^2 values of 25%, 50% and 75% can be regarded as low, moderate and high heterogeneity (8). The following sources of heterogeneity were explored by meta-regression: health status of the population (e.g. CHD or T2D patients), gender, age, MetS definition, study design and ethnicity. In some cases too few studies were available to conduct meta-regression with STATA. In those cases sensitivity analyses were performed. Funnel plots, Egger's and Begg's tests were used to check for publication bias. STATA 11 (StataCorp LP, Collega Station, TX, USA) was used to perform all analyses.

Results

Our literature search yielded 104 articles identified through PubMed and 465 articles identified through Huge Navigator (Fig. 1). None of the studies identified through PubMed was eligible, while 186 identified through Huge Navigator were. Of the eligible papers, 51 were excluded because <2 articles were published on the same gene, and 48 were excluded because all SNPs in the gene described in the article were studied in <4000 subjects. Finally, 87 articles on 25 genes were included in this review. In these 87 articles 88 studies were described.

The majority of the studies were cross-sectional studies ($n = 73$; 83%). Of the remaining studies, 11 were case–control studies, 3 were family studies and 1 was a prospective study. Most studies were either conducted in subjects of Caucasian ($n = 56$; 64%) or Asian origin ($n = 21$; 24%). The average prevalence of MetS across all studies was 30%. In 75% ($n = 66$) of the studies MetS was defined according to the criteria of the NCEP ATP III.

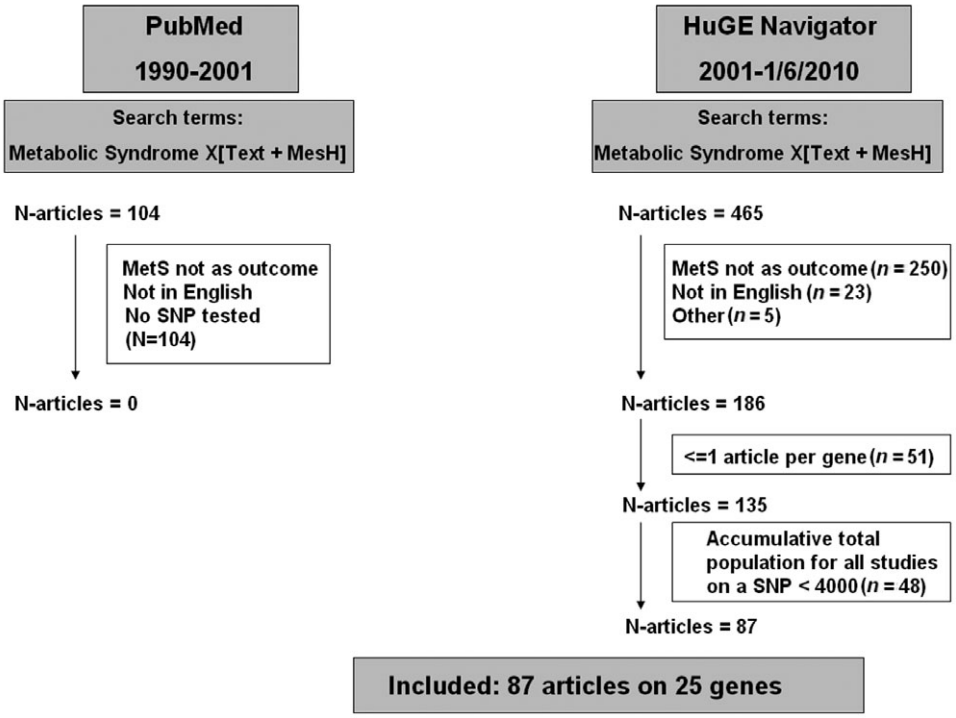

Figure 1 Literature search results. SNP, single nucleotide polymorphism.

Meta-analyses were carried out for those SNPs with three or more eligible studies available in a generally healthy population, which included 37 studies (7,9–43) on nine SNPs located in seven genes (*GNB3*, *PPARG*, *TCF7L2*, *APOA5*, *APOC3*, *APOE*, *CETP*). In none of the meta-analyses the Egger's test, the Begg's test or the funnel plots could indicate the presence of publication bias.

First, we will describe the association between MetS and those genes with sufficient data for meta-analyses. Second, we will describe the remaining SNP–MetS associations in a narrative review. In Table 1, an overview is provided of all genes studied, the pathways they are involved in and the results of the meta-analyses. Detailed information on all studies is available in Table S2.

Results of the meta-analyses

PPARG

PPARG is a nuclear receptor involved in glucose and fatty acid metabolism (22). The Pro12Ala (rs1801282) polymorphism of the *PPARG* gene has been consistently associated with T2D (44,45). However, of the 16 studies investigating the association between Pro12Ala (rs1801282) and MetS (7,11–18,20–22,46,47), most showed no effect (7,9,11–22,46,47). This is confirmed by our meta-analysis among 13 studies (7,9,11–20,22) (pooled OR of Ala vs. Pro 1.08; 95% 0.93–1.24, $I^2 = 48.3\%$) (Fig. 2). Meta-regression revealed that population characteristics such as ethnicity and health status could not explain the moderate heterogeneity present in this meta-analysis (Table S3). Interestingly, although the 12Pro allele is associated with increased risk of T2D and insulin resistance independent of body mass index (BMI) (44), from the meta-analysis it can be concluded that if any effect on MetS exists, 12Ala is the risk allele. As the 12Ala genotype has been associated with BMI in a meta-analysis among Caucasian subjects (44), this effect could possibly be mediated by BMI.

The association between *C1431T* (rs3856806), another well-known *PPARG* polymorphism, and MetS, has been investigated in six cross-sectional studies (22–24,26,28,30) and one family study (47). In the family study, conducted among 423 Chinese subjects, the prevalence of the *1431T* allele was lowest in subjects with MetS. However, in our meta-analysis of the six cross-sectional studies (22–24,26,28,30) there was no association between *C1431T* (rs3856806) and MetS (pooled OR of T vs. C 0.97, 95% CI 0.86–1.11, $I^2 = 0\%$) (Fig. 3).

Interestingly, although both the 12Ala and the *1431C* allele did not seem to increase MetS risk significantly in our meta-analyses, a haplotype containing the same alleles was associated with an increased prevalence of MetS in a cross-sectional study among 1115 French subjects (22). Other SNPs in the *PPARG* gene have not been associated with MetS (27,48).

Table 1 Summary of the reviewed SNPs in relation to metabolic syndrome

Gene – SNPs	Pathways involved					Results	
	Weight regulation	Glucose metabolism	Lipid metabolism	Inflammation	Blood pressure		
Meta-analyses						Pooled OR	I^2 (%)
PPARG							
Pro12Ala (rs1801281)	×	×	×			1.08 (95% CI: 0.93–1.24)	48.3
C134T (rs3856806)						0.97 (95% CI: 0.86–1.11)	0
TCF7L2							
rs7903146		×				1.18 (95% CI 1.04–1.34)	25.6
APOA5							
T113C (rs662799)			×			1.24 (95% CI 1.10–1.41)	47.7
C56G (rs3135506)						1.26 (95% CI 1.09–1.47)	0
APOC3							
C482T (rs2854117)			×			1.57 (95% CI 1.00–2.48)	90.5
C455T (rs2854116)						NA	
APOE							
ε2/ε3/ε4 (ε2/- vs. ε3/ε3)			×			0.91 (95% CI 0.70–1.18)	7.5
ε2/ε3/ε4 (ε4/- vs. ε3/ε3)						1.61 (95% CI 0.87–2.97)	88.3
CETP							
Taq-1B (rs708272)			×			0.93 (95% CI 0.80–1.90)	59.8
						0.89 (95% CI 0.80–0.97)*	4.4
GNB3							
C825T (rs5433)	×		×		×	1.03 (95% CI 0.94–1.12)	0
FTO							
rs9939609	×					1.17 (95% CI 1.10–1.25) (63)	0
Narrative review						Evidence level	
UCP1	×					(–)	
UCP2	×					(–)	
LEPR	×	×	×			(–)	
ADIPOQ							
G276T (rs1501299)		×	×	×		(–)	
IL6							
174G>C (rs1800795)				×		(+)	
RETN							
420C>G (rs1862513)	×			×		(–)	
LMNA							
H566H (rs4641)	×	×	×			(–)	
ADRB2							
Arg16Gly (rs1042713)		×	×		×	(–)	
Gln27Gln (rs1042714)						(–)	
ADRB3							
Trp64Arg (rs4994)		×	×		×	(–)	
PPARD							
87T>C (rs2016520)	×	×				(–)	
PPARGC1A							
Gly482Ser (rs8192678)		×	×			(–)	
Thr394Thr (rs3755863)						(–)	
FABP2							
Ala54Thr (rs179883)		×	×			(–)	
CAPN10							
UCSNP43 (rs3792267)		×				(–)	
IRS1							
Gly927Arg (rs1801278)		×				(–)	
ENPP1							
K21Q (rs1044498)		×				(–)	
GCK							
30G>A (rs1799884)		×				(–)	
KCNJ11							
E23K (rs5219)		×				(–)	

(+), sufficient evidence for an association based on the narrative review; (–), insufficient evidence for an association based on the narrative review.
*Results of a sensitivity analysis in non-patients.
NA, not available; SNP, single nucleotide polymorphism.

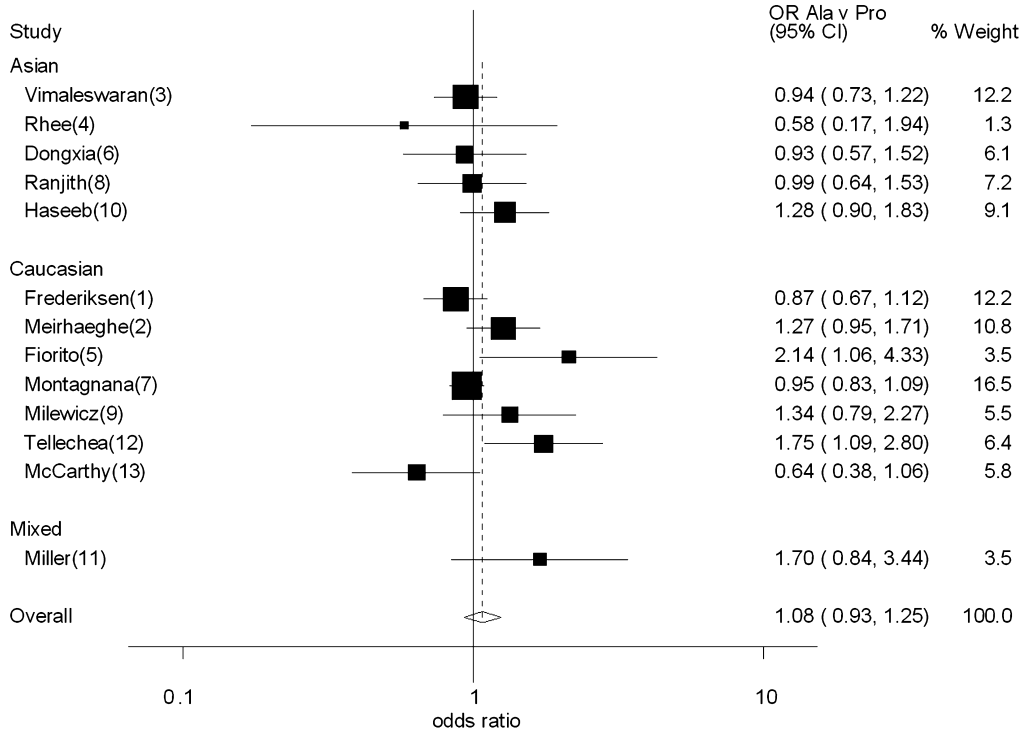

Figure 2 Meta-analysis on the association between the *PPARG* Pro12Ala (rs1801282) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 48.3\%$; MAF Caucasian 0.06–0.17; MAF Asian 0.05–0.13; MAF mixed population 0.09; MAF, minor allele frequency; OR, odds ratio.

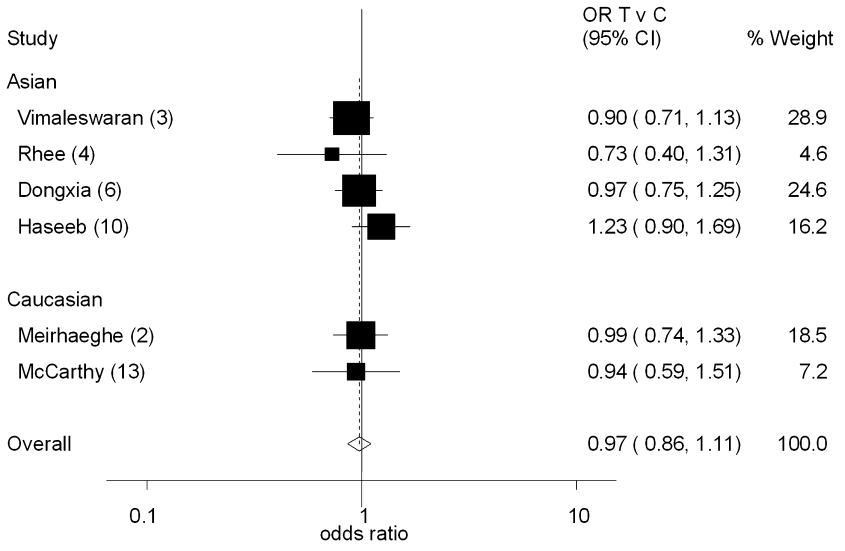

Figure 3 Meta-analysis on the association between the *PPARG C1431T* (rs3856806) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 0\%$; MAF Asian 0.14–0.30; Caucasian 0.08–0.15; MAF, minor allele frequency; OR, odds ratio.

TCF7L2

The *TCF7L2* gene is involved in Wnt signalling and insulin secretion (49). The *T* allele of the rs7903146 polymorphism in the *TCF7L2* gene increases the risk of T2D (50). The *T* allele also increased MetS risk in our meta-analysis of five studies (pooled OR 1.18, 95% CI 1.04–1.34) (Fig. 4) (23–27). The heterogeneity between studies was low ($I^2 = 25.6\%$), and decreased to 0% in a sensitivity analysis among generally healthy subjects (24–27). The pooled OR increased to 1.29 (95% CI 1.10–1.36).

Although both Begg's ($P = 0.01$) and Egger's tests ($P = 0.008$) were significant, no publication bias was present, as the largest studies had the largest effect. One expects that in case of publication bias, the smallest

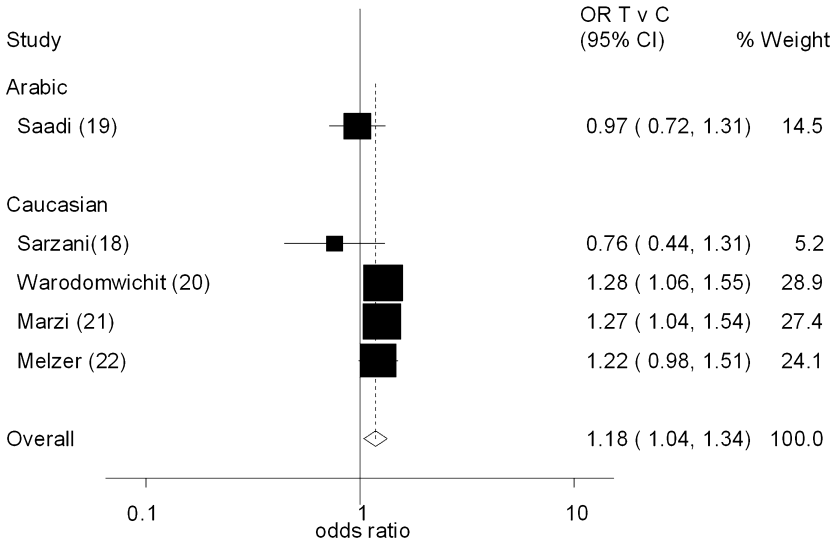

Figure 4 Meta-analysis on the association between the *TCF7L2* rs7903146 polymorphism and the metabolic syndrome; heterogeneity $I^2 = 25.6\%$; MAF Caucasian 0.28–0.35; MAF Arabic 0.39; MAF, minor allele frequency; OR, odds ratio.

studies would show the highest ORs (51,52). A prospective study among 16 143 Swedes confirmed the results of our meta-analysis. In this prospective study the OR for developing MetS in 23 years was 1.10 (95% CI 1.04–1.17) (46).

As expected results for the rs12255372 polymorphism (24–26) were similar as those of the completely correlated rs7903146 polymorphism ($r^2 = 1$ HapMap CEU). Furthermore, in one study among obese hypertensive patients the *TCF7L2* copy number variation, *DG10S478X*, was associated with MetS (23).

APOA5

APOA5 reduces plasma triglyceride levels by stimulating the hydrolysis of triglycerides through the activation of lipoprotein lipase and by inhibiting very low density lipoproteins production (53). The *C* allele of the *T1131C* (rs662799) polymorphism in the *APOA5* gene is associated with higher triglycerides and reduces high-density lipoprotein (HDL) cholesterol levels (54–56). The *T1131C* (rs662799) polymorphism, or genetic variants highly correlated with the *T1131C* (rs662799) polymorphism, were significantly associated with MetS in all (21,28–34,54–56), but three studies (28,31,55). Accordingly, in our meta-analysis among nine of these studies (21,28–34) the *C* allele of the *T1131C* (rs662799) polymorphism increased MetS risks (pooled OR 1.24, 95% CI 1.10–1.41) (Fig. 5). Meta-regression analysis revealed that the moderate heterogeneity ($I^2 = 47.7\%$) present could be explained by population characteristics such as sex and ethnicity (Table S4). Therefore, we performed a sensitivity analysis in Caucasian subjects only. The OR in this sensitivity analysis was somewhat lower (pooled OR *C* vs. *T* 1.20, 95% CI 1.02–1.41, $I^2 = 19.0\%$).

Another *APOA5* polymorphism that has been frequently investigated in relation to MetS is the *C56G* (rs3135506) polymorphism. The meta-analysis included five studies (28,31,32,34) and showed that the *G* allele of the *C56G* (rs3135506) polymorphism increased MetS risk (pooled OR 1.26, 95% CI 1.09–1.47, $I^2 = 0\%$) (Fig. 6). However, the *C56G* (rs3135506) polymorphism was not associated with MetS in a study among 2417 Japanese, which could not be included in the meta-analysis, because the genotype distribution could not be obtained (54).

Three other *APOA5* polymorphisms, all not correlated with one of the polymorphisms discussed above, have also been investigated in relation to MetS (29,31,54). Two of these polymorphisms, *12238T>C* (rs625524) (29) and Gly185Cys (rs2075291) (54), were associated with MetS, in one single study.

APOC3

APOC3 increases plasma triglycerides levels, by the inhibition of lipoprotein lipase activity and by the interference with ApoE-mediated uptake of triglycerides (48,57). The minor *482T* allele of the *APOC3 C482T* (rs2854117) polymorphism is associated with increased triglyceride levels (58). The same allele also increased MetS risk in four (18,34,35,48) out of five studies (18,29,34,35,48). Our meta-analysis among the four studies with genotype distributions available (18,29,34,35) confirmed that the *482T* allele increased MetS risk (pooled OR 1.57, 95% CI 1.00–2.48) (Fig. 7). However, although the direction of the effect was the same for most studies, the heterogeneity between studies was high ($I^2 = 90.5\%$). Both the heterogeneity and the OR were slightly lower among cross-sectional studies (OR 1.24, 95% CI 0.90–2.01, $I^2 = 78.2\%$) (29,35) and

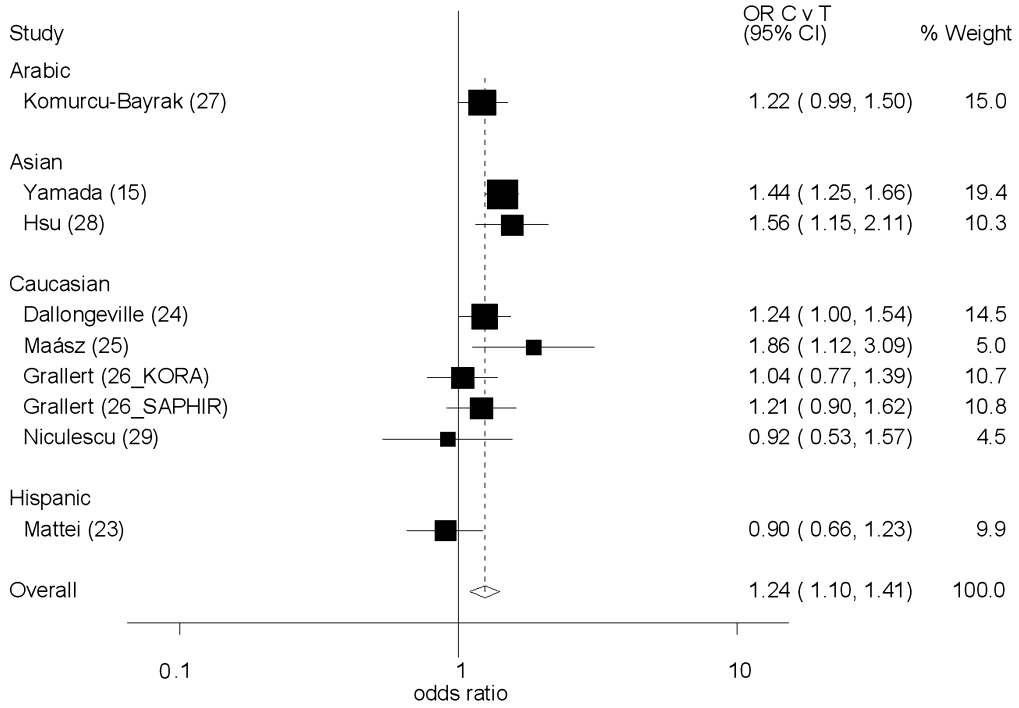

Figure 5 Meta-analysis on the association between the *APOA5 T1131C* (rs662799) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 47.7\%$; MAF Arabic 0.13; MAF Asian 0.30–0.31; MAF Caucasian 0.06–0.08; MAF Hispanic 0.14; MAF, minor allele frequency; OR, odds ratio.

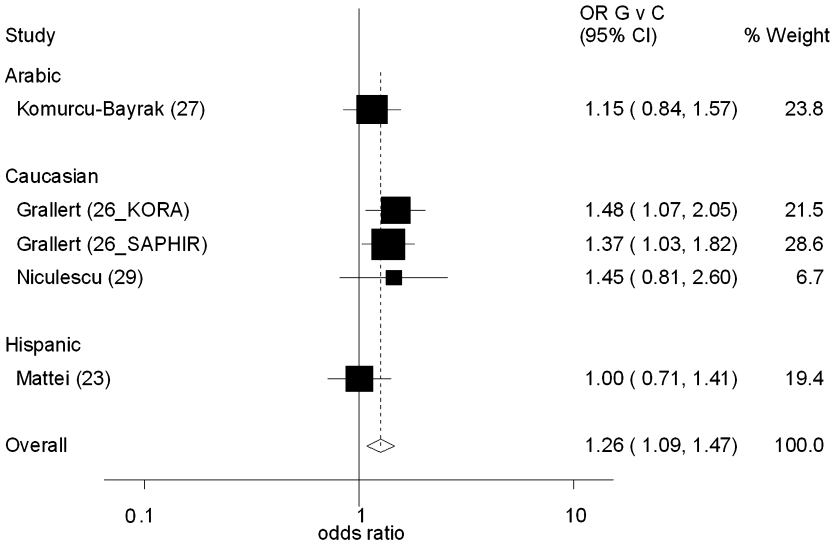

Figure 6 Meta-analysis on the association between the *APOA5 C56G* (rs3135506) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 0\%$; MAF Arabic 0.05; MAF Caucasian 0.06–0.09; MAF Hispanic 0.10; MAF, minor allele frequency; OR, odds ratio.

studies in Caucasian subjects (OR 1.16, 95% CI 0.79–1.70, $I^2 = 84.9\%$) (29,34,35).

As expected results for the *C455T* (rs2854116) polymorphism (18,34,35,48,59) were similar to those of the highly correlated *C482T* (rs2854117) polymorphism ($r^2 = 0.97$ HapMaP CEU) (35). On the contrary, for *APOC3 1100C>T* (15) and *APOC3* SstI (20,29) no association with MetS could be detected.

APOE

Apolipoprotein-E (APOE) has an important function in the clearance of chylomicron remnants and very low density lipoproteins from plasma. Three APOE isoforms encoded by the ε2/ε3/ε4 haplotype exist. The ε3 isoform is the most prevalent isoform. In comparison with the ε3 isoform, the ε2 isoform decreases cholesterol levels and increases triglyceride levels, whereas the ε4 isoform increases both

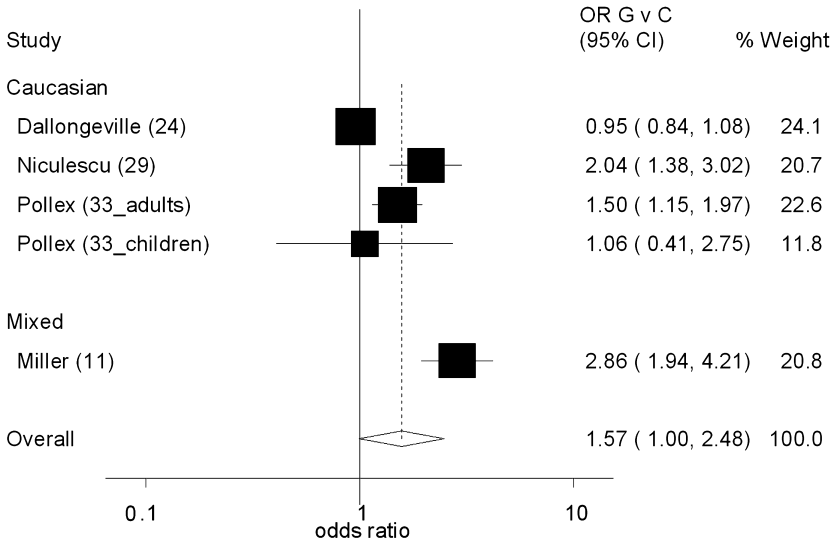

Figure 7 Meta-analysis on the association between the *APOC3 C482T* (rs2854117) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 90.5\%$; MAF mixed population 0.24; MAF Caucasian (excluding Oji Cree aboriginals33) 0.21–0.27; MAF Oji Cree aboriginals33 0.43–0.44; MAF, minor allele frequency; OR, odds ratio.

cholesterol and triglyceride levels (60). In our meta-analysis among five studies (18,36–38,43) the ε2/- genotype (ε2/ε3 + ε2/ε2) none significantly decreased MetS risk (pooled OR ε2/- vs. ε3/ε3 0.91; 95% CI 0.70–1.18, $I^2 = 7.5\%$) whereas the ε4/- genotype (ε4/ε4 + ε4/ε3) tended to increase MetS risk (pooled OR ε4/- vs. ε3/ε3 1.61, 95% CI 0.87–2.97, $I^2 = 88.3\%$) (Fig. 8). The fact that four out of five studies were conducted in subjects of different ethnicity may explain the high heterogeneity ($I^2 = 88.3\%$) observed for the ε4/- genotype.

In two studies the effect of individual SNPs in the *APOE* gene instead of the effect of the ε2/ε3/ε4 haplotype was investigated. In a study among 1788 Japanese (21), in which three SNPs of the APOE gene had been genotyped, the Arg158Cys (rs7412) polymorphisms, which is part of the ε2/ε3/ε4 haplotype, was associated with MetS. However, this association could not be replicated in 305 Caucasian coronary artery disease patients (20).

CETP

The cholesteryl ester transfer protein (CETP) plays an import role in reverse cholesterol transport. The B2 allele of the *CETP* Taq-1B (rs708272) polymorphism increases HDL cholesterol levels and decreases triglyceride levels and CETP activity (61). In our meta-analysis including four studies (36,39–41), the B2 allele tended to decrease MetS risk (pooled OR 0.93, 95% 0.80–1.09, $I^2 = 59.8\%$.) (Fig. 9). When we excluded the study of Ranjith *et al.* (36) among 592 patients with acute MI from our meta-analysis the heterogeneity decreased ($I^2 = 4.4\%$), and the OR became significant (pooled OR B2 vs. B1 0.89, 95% CI 0.80–0.97). The study among 1788 Japanese, which could not be included in the meta-analysis, showed no association between the Taq-1B (rs708272) polymorphism and MetS (54). Furthermore, in studies on other polymorphisms in the *CETP* gene, no associations with MetS were observed (20,21,54).

FTO

Studies in humans and rodents suggest that FTO regulates food intake and effects the lypolytic activity in adipose tissue (62). The *A* allele of the rs9939609 polymorphism in the *FTO* gene has been associated with increased BMI and T2D risk in multiple genome wide association studies (GWAS) (63). The *A* allele of the rs9939609 also increased MetS prevalence in a large meta-analysis among 12555 European subjects (OR per A allele 1.17; 95% CI 1.10–1.25, $P = 3.0 \times 10^{-6}$) (63) and in a smaller meta-analysis among 2112 subjects of mixed ethnicity (*AA* + *AT* vs. *TT* OR 1.26; 95% CI 1.02–1.57) (64). ORs of the individual studies included in the meta-analyses ranged from 1.10 to 1.44. In line with these results, the OR per *A* allele for developing MetS in 23 years was 1.08 (95% CI 1.02–1.14) in a large prospective study among 16 143 non-diabetic Swedes (46). Furthermore, the rs1421085 polymorphism, which is highly correlated with the rs9939609 polymorphism ($r^2 = 0.93$), was associated with MetS in two independent studies (65,66). On the contrary, rs9939609 and two other highly correlated polymorphisms were not associated with MetS in a study among 1488 Japanese (67).

GNB3

The *GNB3* gene is involved in G-protein signal transduction. The *C825T* (rs5433) polymorphism in the *GNB3* gene has been associated with obesity, hypertension, dyslipidaemia and T2D, which are all features of MetS (10,42). However, although in one study the *C825T*

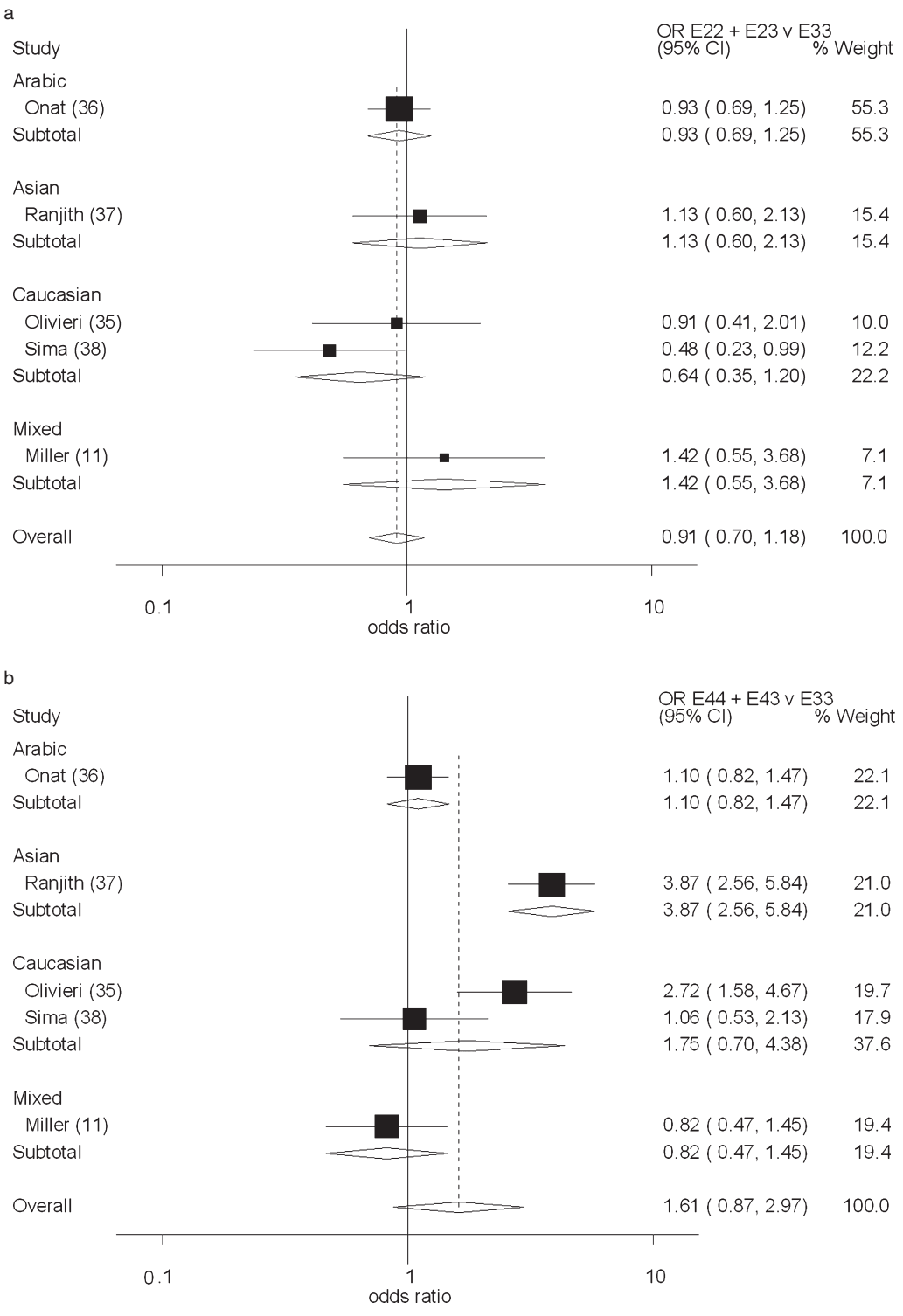

Figure 8 (a) Meta-analysis on the association between the *APOE* ε2/ε3/ε4 haplotype and the metabolic syndrome; heterogeneity $I^2 = 7.5\%$; frequency ε2 Arabic 0.12; frequency ε2 Asian 0.05; frequency ε2 Caucasian 0.06–0.09; frequency ε2 mixed 0.05; OR, odds ratio; (b) meta-analysis on the association between the *APOE* ε2/ε3/ε4 haplotype and the metabolic syndrome; heterogeneity $I^2 = 88.3\%$; frequency ε4 Arabic 0.07; frequency ε4 Asian 0.09; frequency ε4 Caucasian 0.08–0.09; frequency ε4 mixed 0.20; OR, odds ratio.

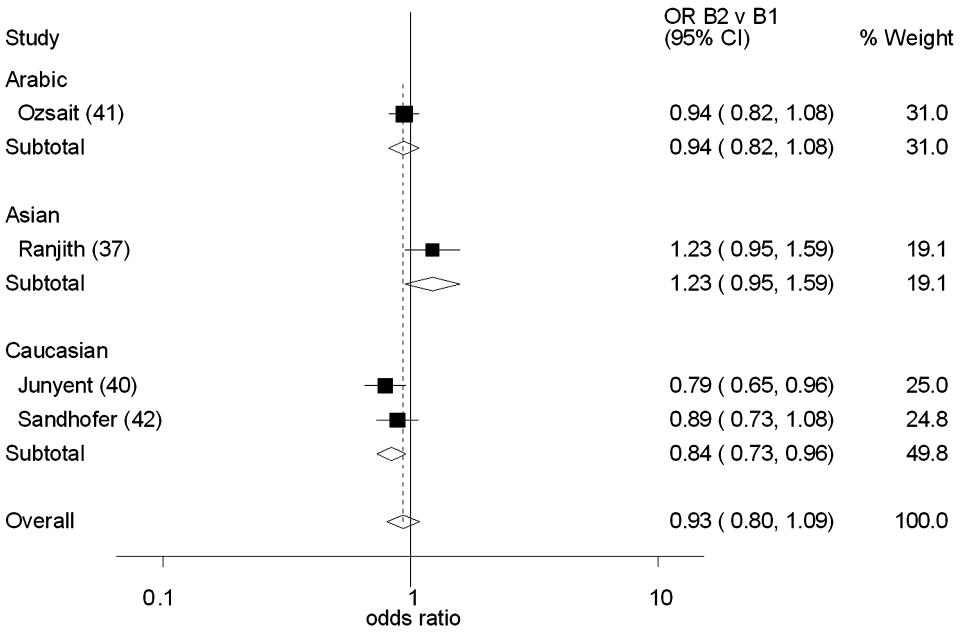

Figure 9 Meta-analysis on the association between the *CETP* Taq-1B (rs708272) polymorphism and the metabolic syndrome; heterogeneity $I^2 = 59.8\%$; MAF Arabic 0.43; MAF Asian 0.48; MAF Caucasian 0.41–0.43; MAF, minor allele frequency; OR, odds ratio.

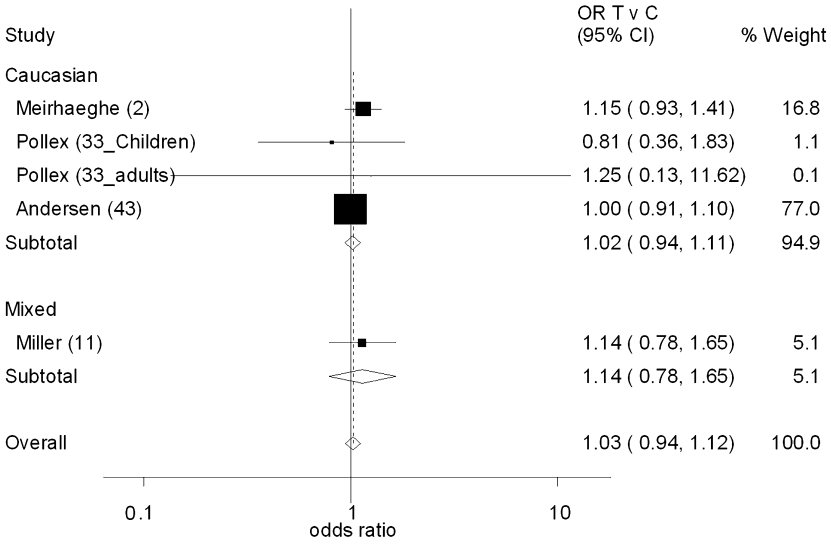

Figure 10 Meta-analysis on the association between the *GNB3 C825T* (rs5433) and the metabolic syndrome; heterogeneity $I^2 = 0\%$; MAF mixed 0.34; MAF Caucasian (excluding Oji Cree aboriginals33) 0.31–0.34; MAF Oji Cree aboriginals33 0.46–0.49; MAF, minor allele frequency; OR, odds ratio.

(rs5433) polymorphism was associated with MetS in Oji Cree women (35), other studies could not replicate these results (10,18,21,42). Also, our meta-analysis of four studies (10,18,35,42) (Fig. 10) could not demonstrate an association between the *C825T* (rs5433) polymorphism and MetS (pooled OR of *825T* vs. *C* 1.03, 95% CI 0.94–1.12, $I^2 = 0$). In one study, among 2417 Japanese, the association with the *GNB3 1429C>T* (rs5446) polymorphism was investigated (54). Also this polymorphism was not associated with MetS.

Narrative review of associations with metabolic syndrome for single nucleotide polymorphisms not eligible for meta-analysis

In this narrative review we describe SNPs that were not eligible for meta-analysis because they have been studied in too few studies with generally healthy subjects. Detailed information about these SNPs can be found in Table S2i–y.

Of all SNPs, the strongest evidence for an association with MetS was found for the *IL6 174G>C* (rs1800795)

promoter polymorphism. IL-6 is a cytokine with a broad range of effects, e.g. it is the primary determinant of hepatic CRP secretion (68). Elevated plasma IL-6 levels are associated with T2D and CHD, both end stages of MetS (68). The association between the *IL6 174G>C* (rs1800795) promoter polymorphism and MetS was significant in three (20,68,69) out of four (20,68–70) studies. In three studies the *174C* allele increased MetS risk (68–70), while in a fourth study the direction of the association was not reported (20). In most studies on inflammatory SNPs other than *IL6 174G>C* (rs1800795), such as SNPs in *RETN* (21,71,72) and *ADIPOQ* (54–58,73,74), no association with MetS was found. Especially for *ADIPOQ* this was remarkable. The *ADIPOQ* gene encodes for adiponectin. Lower plasma adiponectin concentrations have been associated with several features of MetS including insulin resistance (75). Furthermore, in a linkage study the *ADIPOQ* locus, 3q27, was associated with MetS (76). However, in most studies the *ADIPOQ G276T* (rs1501299) polymorphism was not associated with MetS (75,77–79). Furthermore, in the single study in which an effect was shown for *ADIPOQ G276T* (rs1501299) (80), this effect was opposite to the effect expected based on the association of *ADIPOQ G276T* (rs1501299) with adiponectin and insulin sensitivity (81). The *ADIPOQ G276T* (rs1501299) polymorphism was not the only SNP in which, despite strong prior evidence for possible involvement of the gene in MetS development, an association with MetS seemed absent. Also, no association with MetS seemed to exist for SNPs in the *LMNA* (82–85) gene, while the *LMNA* gene is associated with lipodystrophy, a syndrome that shares many features with MetS (82).

Involvement of a gene in multiple MetS pathways did not guarantee an association for SNPs in this gene with MetS. The evidence for an association with MetS was weak for SNPs in the *ADRB2* (20,21,46,86) and *ADRB3* (21,46,87–89) gene, genes involved in glucose metabolism, lipid metabolism and blood pressure regulation (86), SNPs in the *LEPR* gene (54,90,91), which is involved in body weight regulation, fatty acid oxidation and glucose metabolism (92); SNPs in the *PPARD* gene (21,93,94), which regulates both glucose and energy metabolism (94); and SNPs in the *PPARGC1A* gene (11,21,46,95), which is involved in lipid and glucose metabolism (95). However, for the Ala54Thr (rs1799883) SNP (18,35,48,96–98) in the *FABP2* gene, which is involved in both fatty acid and glucose metabolism (96,97), some evidence for an association with MetS exists. In the majority of studies (18,35,96–98), most of which were conducted in patient populations (48,96–98), the Thr54 allele increased MetS risk, although in most studies the association was not statistically significant (18,35,96,98). For all other SNPs reviewed, either located in genes involved in energy metabolism (*UCP1* and *UCP2* (11,21,46,54,99–101)) or in genes involved in glucose metabolism (*CAPN10* (21,46,102–105), *IRS1* (15,21,46), *ENPP1* (21,46,106–108), *GCK* (21,109) and *KCNJ11* (15,21,46)) the evidence for an association with MetS was not substantial.

Discussion

In this systematic review we described the most studied SNPs in relation to MetS. The overall results suggest an association with MetS for SNPs in the *FTO*, *TCFL72*, *IL6*, *APOA5*, *APOC3* and *CETP* genes.

The *FTO* rs9939609 and the *TCF7L2* rs7903146 polymorphism are the top hits of GWAS on respectively BMI (110) and T2D (111). The *TCF7L2* rs7903146 polymorphism influences insulin secretion, and to a lesser extent this SNP also affects insulin resistance (112). The *174C* allele of the *IL6 174G>C* (rs1800795) polymorphism increased MetS risk in three (20,68,69) out of four studies (20,68–70). In line with the effect on MetS the *174CC* genotype tended to increase BMI and IL6 levels (113), both MetS-associated features, in meta-analysis on 15 and 17 studies, respectively. Accordingly, in another meta-analysis on seven studies the *174CC* genotype also tended to increase CHD risk, an end stage of MetS (114). However, contrary to the effect on MetS, the *174CC* genotype significantly decreased glucose levels in a meta-analysis on seven studies (113). The other SNPs that were associated with MetS, the *T1131C APOA5* (rs662799) (31), the *C56G APOA5* (rs3135506) (31), the *C455T* (rs2854116) *APOC3*, the *C482T* (rs2854117) *APOC3* (58) and the Taq-1B (rs708272) *CETP* (61) polymorphisms are all associated with hypertriglyceridaemia. Furthermore, the *C482T* (rs2854117) polymorphism, which is located in the insulin response element of the *APOC3* gene promoter, has also been associated with insulin and glucose levels (57,115).

Focussing on combined phenotypes, like MetS, may lead to the discovery of new SNPs that would not have been found when studying the phenotypes separately. The fact that the study of combined phenotypes may lead to the discovery of new risk loci is nicely illustrated by a recent GWAS on Crohn's and Celiac disease, where the focus on risk loci shared between Crohn's and Celiac disease leads to the discovery of six new risk loci (116). All SNPs included in this review that were associated with MetS were also strongly associated with an individual feature of MetS. Up till now no SNP has been found, which has only a minor effect on individual MetS features, but which does affect the clustering of the different features. Nevertheless, such a SNP may still be discovered. Interestingly, we observed that although all SNPs associated with MetS were associated with an individual MetS feature the reverse is not always true. For example, both *PPARG* Pro12Ala (rs1801282) and *TCF7L2* rs7903146 are associated with hyperglycae-

mia. However, only *TCF7L2* rs7903146 and not *PPARG* Pro12Ala (rs1801282) seemed to be associated with MetS. This subdivision of on the one hand SNPs that are associated with one MetS feature only, and on the other hand SNPs that are associated with multiple MetS features, and thus also associated with MetS, may facilitate the discovery of pathways responsible for the clustering of MetS features.

Interestingly, although disturbances in glucose metabolism (1), weight regulation (1) and inflammation (117) all three have been proposed to initiate MetS, most SNPs associated with MetS are located in genes involved in lipid metabolism. The associations of these SNPs in the *CETP*, *APOC3* and *APOA5* genes with the MetS may be mediated by hypertriglyceridaemia. Accumulation of triglycerides in the muscles may stimulate the development of insulin resistance (118). Furthermore, dysfunctioning of the *APOA5* and *APOC3* genes increases free fatty acid levels (57,119), which in turn may stimulate development of MetS features, such as dyslipidaemia, overweight, insulin resistance, hypertension or inflammation (118). Alternatively, the overrepresentation of SNPs in lipid metabolism may be caused by the stress put on lipid metabolism in MetS definition. In the most common MetS definitions, the NCEP ATP III and the IDF definition, a disturbed lipid metabolism is characterized by two MetS features, i.e. low HDL cholesterol levels and increased triglyceride levels, whereas disturbances in the other mechanisms such as weight regulation are all only characterized by one MetS feature.

In this review we have focussed on SNP–MetS associations, which have been investigated in at least two studies. Consequently, significant SNP–MetS associations that have not been researched yet or that have only been researched in one study were not described. One of the best ways to test a large number of not investigated SNP–MetS associations is to conduct a GWAS. Unfortunately, to the best of our knowledge, such a GWAS has not been conducted yet.

Strength of this review is the unbiased way in which we have summarized results of the available studies on SNP–MetS associations. For all genes described, at least one SNP–MetS association was investigated in an accumulative total population across all published studies ≥4000 subjects. The number of 4000 subjects allowed us to detect SNP–MetS associations of moderate effect size (OR ≤0.8 or an OR ≥1.2). Therefore, we may have missed associations of smaller effect size. For example, the pooled OR of 0.90 for the APOE ε2ε3ε4 haplotype was not statistically significant in our meta-analysis. Population characteristics, such as ethnicity and health status of the study population, differed between the studies included in this review. Despite these differences, study outcomes were homogeneous for some SNPs, e.g. the *GNB3 C825T* (rs5433) and *PPARG C1431T* (rs3856806) polymorphism. However, for other SNPs these differences could explain the observed heterogeneity in study outcomes. For example, ethnicity explained nearly all heterogeneity present in the meta-analysis on *APOA5 T1131C* (rs662799). Furthermore, heterogeneity decreased and the OR increased, if studies in patient populations were excluded from the meta-analyses on the *TCF7L2* rs7903146 and the *CETP Taq-1B* (rs708272) polymorphisms. In two meta-analyses, on the *APOC3 C482T* (rs2854117) polymorphism and *APOE* ε2ε3ε4 haplotype, a high unexplained heterogeneity was present. Especially for these genetic variants it will be valuable to conduct an updated meta-analysis stratified for several subgroups, if more studies become available. The Egger's and Begg's tests did not indicate that in any of the meta-analyses publication bias was present. However, both tests have a low power unless a large number of studies ($n \geq 25$) are analysed (51,52). As our meta-analyses were conducted among a smaller number of studies, we can not rule out the possibility that publication bias is present anyway.

In conclusion, we found evidence for an association with MetS for eight SNPs. All of these SNPs were also associated with an individual MetS feature, most of them with dyslipidaemia. This suggests that lipid metabolism plays a central role in MetS development.

Conflict of Interest Statement

No conflict of interest was declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The definitions of the MetS according to WHO, EGIR, NCEP ATP III, IDF and AHA-NHLBI.
Table S2. Studies on genetic variants and the metabolic syndrome.
Table S3. Meta-regression on the LN(OR) of the *PPARG Pro12Ala* (rs1801282) polymorphism on the metabolic syndrome.
Table S4. Meta-regression on the LN(OR) of the *APOA5 T1131C* (rs662799) polymorphism on the metabolic syndrome.

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