The cardiovascular metabolic syndrome
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Citation for published version (APA):

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Metabolic Syndrome and Risk of Coronary, Cerebral and Peripheral Vascular Disease in a Large Dutch Population with Familial Hypercholesterolemia
Abstract

Background:
The increased risk of cardiovascular disease (CVD) due to the presence of metabolic syndrome is becoming increasingly important. However, there is paucity of data with regards to the consequences of metabolic syndrome, specifically on the risk of cerebrovascular (CeVD) and peripheral vascular disease (PVD), in addition to coronary heart disease (CHD) in populations with a priori elevated CHD risk.

Methods:
We studied 2400 patients with Familial Hypercholesterolemia and 112,943 person years of follow-up from 27 Dutch lipid clinics. We required data on all five risk factors to determine a diagnosis of metabolic syndrome as per modified National Cholesterol Education Program Adult Treatment Panel III definition. Such data were available for 1698 patients.

Results:
Metabolic syndrome (presence of ≥ 3 risk factors) was present in 39 % (n= 657) patients. Patients with metabolic syndrome had higher incidence of CHD (34% vs 20 %), CeVD (4.4% vs 2.5 %), PVD (6.2% vs 2.9 %) and total CVD (39% vs 24%), as compared to patients without metabolic syndrome. Multivariable Cox regression analyses, controlling for age, gender, smoking, LDL cholesterol level and statin therapy, showed that there was significantly higher risk among patients with metabolic syndrome for CHD (RR 1.54, 95% CI 1.23- 1.94); PVD (RR 1.97, 95% CI 1.13-3.45) and total CVD (RR 1.50 95% CI 1.21-1.85). The result for CeVD however did not reach statistical significance (RR 1.54 CI 0.88-3.05).

Conclusion:
In a population of patients with Familial Hypercholesterolemia, metabolic syndrome is not only associated with increased total cardiovascular disease but also with peripheral vascular disease and coronary heart disease.
Background

The prevalence and risk associated with metabolic syndrome is becoming increasingly important (1). Various studies in recent years have reported that the metabolic syndrome is associated with an increase in cardiovascular disease (CVD) (2-15). A recent meta-analysis by Ford (16) showed that among patients with metabolic syndrome, random-effect estimates of combined relative risk amounted to 1.65 for cardiovascular disease. However, there is still an uncertainty about the clinical importance and consequences of the metabolic syndrome (17).

In addition, studies in various population subgroups may be helpful in assessing how well the metabolic syndrome predicts risk for future adverse health events (16). There is paucity of data with regards to the consequences of metabolic syndrome specifically on cerebrovascular (CeVD) and peripheral vascular disease (PVD). There are very few studies that have looked separately into effect of metabolic syndrome on disease parameters of CeVD (9, 12, 18, 19) or PVD.

Heterozygous Familial Hypercholesterolaemia (FH) is a common hereditary disorder of lipoprotein metabolism (prevalence 1:400). The disorder is caused by mutations in the low-density lipoprotein receptor (LDL-R) gene. Previously we have shown contribution of some the classical risk factors such as male gender, smoking, hypertension, diabetes mellitus, HDL cholesterol and lipoprotein(a) levels to be important for CVD in 2400 Dutch FH patients (20).

In this study we will look at the prevalence and risk associated with the metabolic syndrome for coronary, cerebral and peripheral vascular disease in this population which includes patients inducted from 27 clinics around the Netherlands.
Methods

Study design and study population

Routinely, lipid clinics in the Netherlands submit DNA samples from clinically suspected FH patients to a central laboratory for LDL-receptor mutation analysis. This laboratory, located at the Academic Medical Centre of the University of Amsterdam, has been appointed the molecular diagnostic centre for nationwide FH screening in the Netherlands. Since 1989, the DNA bank database has collected over 9300 samples from more than 60 lipid clinics. At the start of the current study in 1999, we randomly selected 4000 hypercholesterolaemic patients from this database with the aid of a computer program (Microsoft Excel).

A team of 13 trained data collectors visited the 27 clinics and reviewed 4000 patient records (see below). A total of 2400 patients fulfilled the diagnostic criteria for FH and were included in the study. The inclusion and exclusion criteria for participation in the study are outlined in Table 1 and discussed in detail previously (20). The FH diagnostic criteria were based on criteria used in the US (the MedPed criteria), the UK (the Simon Broome Register criteria) and the Netherlands (the Dutch Lipid Clinic Network criteria). To prevent selection bias, we selected only those patients from the 48 larger outpatient clinics which are characterized by clinically more diverse patient populations. Patients

<table>
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<tr>
<th>Table 1</th>
<th>Inclusion and exclusion criteria for Familial Hypercholesterolemia (FH) population.</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>Males and females</td>
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<tr>
<td>Age 18 years and older</td>
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<tr>
<td><strong>FH diagnostic criteria</strong></td>
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<tr>
<td>I. Presence of a documented LDL-receptor mutation</td>
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<tr>
<td>Or</td>
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<tr>
<td>II. LDL cholesterol level above the 95th percentile for sex and age, in combination with at least one of the following</td>
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<tr>
<td>(a) the presence of typical tendon xanthomas in the patient or in a first-degree relative</td>
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<tr>
<td>(b) an LDL cholesterol level above the 95th percentile for age and sex in a first-degree relative</td>
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<tr>
<td>(c) proven coronary artery disease in the patient or in a first-degree relative under the age of 60 years</td>
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<table>
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<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Secondary causes of hypercholesterolaemia such as renal, liver or thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia caused by other genetic defects, such as familial defective apolipoprotein B</td>
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from smaller lipid clinics were not selected for the study, as these clinics normally only send DNA samples of the rare, usually very serious FH cases. Ultimately, the randomly selected patients were derived from 27 lipid clinics throughout the Netherlands.

**Pilot study**

In a pilot study, the feasibility of the study was assessed by reviewing 100 medical records at four different hospitals. The availability and quality of the medical record data were tested and subsequently the case record forms were improved where necessary. Data on risk factors were present in more than 80% of the records and this was considered to be sufficient. Only smoking habits proved to be not adequately documented (56%), and additional questionnaires were designed for this topic.

**Data collection**

The above-mentioned trained team of data collectors scrutinized the 2400 patients’ medical records for extensive clinical information (demographics, classical risk factors, laboratory parameters and CVD events) recorded until the last lipid clinic visit. To ensure data completeness, additional information was sought from general practitioners, the patients themselves, and hospitals that patients had visited formerly. If any of these sources reported a CVD event or death that had occurred up until 1 year after the last lipid clinic visit, this was recorded in the case record form. To obtain consistent datasets, quality guidelines were implemented (21). All data collectors underwent extensive training; handbooks with clinical definitions were used and interobserver studies were carried out. Questionnaires and study information were sent by mail. Written informed consent was obtained from all living patients. The Ethics Institutional Review Board of each participating hospital approved the protocol.

**Laboratory parameters**

Lipid levels, as stated in the medical record, were determined in fasting patients not using lipid-lowering medication for at least 6 weeks. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured by standard methods. LDL-C was calculated with the Friedewald formula. The DNA samples were screened for the presence of LDL-R mutations, as published previously (22).
**Metabolic syndrome**

Metabolic syndrome will be defined as per National Cholesterol Education Program (NCEP) guidelines (23). Use of a recently modified definition of impaired fasting glucose to include persons with a level of 100 mg/dL or higher would be used (24). A recent NHANES III analysis suggested that a waist circumference of 102 cm in men corresponded to a body mass index of about 28 kg/m2 and a waist circumference of 88 cm in women to a body mass index of 24–26 kg/m2 (25). Therefore, we considered a body mass index of ≥30 kg/m2 in men and ≥25 kg/m2 in women as evidence of excess weight.

A diagnosis requires the concomitant presence of 3 or more of the following risk factors. 
1. Elevated triglycerides (≥150 mg/dL [≥1.7 mmol/L])
2. Low HDL cholesterol (men <40 mg/dL [<1.03 mmol/L]; women <50 mg/dL [<1.29 mmol/L])
3. Fasting glucose ≥5.55 mmol/L (≥100 mg/dL)
4. Systolic blood pressure (BP) ≥130 mmHg and/or diastolic BP ≥85 mmHg
5. Increased waist circumference (men >40 inches [≥102 cm]; women >35 inches [≥88 cm]) or BMI ≥ 30 kg/m² for men and ≥ 25 kg/m² for women.

**Disease endpoints**

The combination of cardiovascular mortality and CVD was the primary measure of outcome (total CVD). Total CVD was defined by the presence of at least one of the following:

**A. Coronary Heart Disease (CHD)**

CHD was defined if any one of the following present (I) myocardial infarction, proven by at least two of the following: (a) classical symptoms (>15 min), (b) specific electrocardiographic abnormalities, (c) elevated cardiac enzymes (>2x upper limit of normal); (II) percutaneous coronary intervention or other invasive procedures; (III) coronary artery bypass grafting; (IV) angina pectoris, diagnosed as classical symptoms in combination with at least one unequivocal result of one of the following: (a) exercise test, (b) nuclear scintigram, (c) dobutamine stress ultrasound, (d) a more than 70% stenosis on a coronary angiogram;
B. Cerebrovascular Disease (CeVD)
CeVD was defined if anyone of the following present, (V) ischaemic stroke, demonstrated by CT- or MRI scan; (VI) documented transient ischaemic attack.

C. Peripheral Vascular Disease (PVD)
PVD was defined if any one of the following present (VII) peripheral arterial bypass graft; (VIII) peripheral percutaneous transluminal angioplasty or other percutaneous invasive intervention; (IX) intermittent claudication defined as classical symptoms in combination with at least one unequivocal result of one of the following: (a) ankle/arm index <0.9 or (b) a stenosis (>50%) on an angiogram or duplex scan. If information on CVD did not strictly fulfill the above-mentioned criteria, or if any suspect history, symptoms or diagnostic evaluations were found in the record, the case was presented to an independent adjudication committee.

Statistical analyses
Differences in clinical characteristics between patients with and without metabolic syndrome will be tested with chi-square statistics or independent sample t-test. In case of a skewed distribution, the t-test will be performed on log-transformed, whilst medians and interquartile ranges are presented. To adjust for the effects of age and gender we used multiple logistic regression and univariate general linear modelling. Cox proportional hazard regression analysis was used to assess the association of metabolic syndrome with the occurrence of CVD in multivariate analyses. Follow-up started at birth and ended for each individual at the date of the first occurrence of established CVD. Patients without CVD were censored at the date of the last lipid clinic visit or at the date of death attributable to other causes. The following variables were entered into the analyses: age, gender, smoking (time-dependent), LDL cholesterol, statin therapy. For smoking we implemented a linearly decreasing risk effect for the 3 years after cessation (26). Analyses were performed using SPSS (version 10.1, Chicago, IL, USA) and SAS software (version 8.02, Cary, NC, USA). A P-value of <0.05 was considered to be statistically significant.
Chapter 12

Results

Out of 2400 patients with FH, we had all five variables to make a diagnosis metabolic syndrome in 1698 patients. Of these, metabolic syndrome was present in 31% of the population. Of those with metabolic syndrome, females had a slightly higher prevalence (53%). Patients with metabolic syndrome were more likely to be older, have higher BMI, have diabetes and higher prevalence to be on statin therapy as compared to patients without metabolic syndrome (Table 2). Prevalence of overt diabetes was low (5.4% among those with metabolic syndrome and 0.4% among without metabolic syndrome). Among patients included in the present study 501 (29.5%) patients had at least one cardiovascular event. A higher number of patients with metabolic syndrome suffered from any CVD (39%) vs those without metabolic syndrome (24%; p < 0.05). Similarly patients with metabolic syndrome had higher rates of CHD (34% vs 20%), CeVD (4.4 vs 2.5%), and PVD (6.2% vs 2.9%).

Table 2. Baseline Characteristics by Metabolic Syndrome Status in 1698 Patients with Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Metabolic Syndrome</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Age, (years; ± SD)</td>
<td>n=1041 (69%)</td>
<td>n=657 (31%)</td>
</tr>
<tr>
<td>BMI (kg/m² ± SD)</td>
<td>42 (12)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>Female Gender (%)</td>
<td>24.1 (3.0)</td>
<td>27.1 (3.6)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>508 (49)</td>
<td>351 (53)</td>
</tr>
<tr>
<td>Current Smoking (%)</td>
<td>4 (0.4)</td>
<td>35 (5.4)</td>
</tr>
<tr>
<td>Family History of MI (%)</td>
<td>561 (54)</td>
<td>362 (55)</td>
</tr>
<tr>
<td>Statin therapy (%)</td>
<td>304 (29)</td>
<td>252 (38)</td>
</tr>
</tbody>
</table>

BMI=body mass index

In the multivariate Cox regression model, we adjusted for age, gender, smoking, LDL cholesterol and statin therapy. Table 3 shows that patients with metabolic syndrome were at an increased risk of CHD (RR 1.54; 95% CI 1.23-1.94) and PVD (RR 1.97; 95% CI 1.13-3.45). For CeVD the results were not significant, however when looking at combined cardiovascular risk, again patients with metabolic syndrome were at a higher risk.
Table 3. Relative Risks of Cardiovascular Events According to Presence of Metabolic Syndrome (n=1698)

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Absent n = 1041 (61%)</th>
<th>Present n = 657 (39%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>209 (20)</td>
<td>225 (34)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td>CeV D</td>
<td>26 (2.5)</td>
<td>29 (4.4)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>PVD</td>
<td>30 (2.9)</td>
<td>41 (6.2)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>Total CVD</td>
<td>245 (24)</td>
<td>256 (39)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>49%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, smoking, LDL cholesterol, statin therapy. Coronary Heart Disease (CHD); Cerebrovascular Disease (CeV D); Peripheral Vascular Disease (PVD); Cardiovascular disease (CVD).

Table 4. Relative Risks According to Number of Risk Factors of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Number of risk factors present</th>
<th>0 (n=149 (%))</th>
<th>1-2 (n= 892 (%))</th>
<th>≥3 (n= 657 (%))</th>
<th>Overall ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>15 (10)</td>
<td>194 (22)</td>
<td>225 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CeV D</td>
<td>4 (3)</td>
<td>22 (3)</td>
<td>29 (4)</td>
<td>0.29</td>
</tr>
<tr>
<td>PVD</td>
<td>0 (0)</td>
<td>30 (3)</td>
<td>41 (6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total CVD</td>
<td>19 (13)</td>
<td>226 (25)</td>
<td>256 (39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, smoking, LDL cholesterol and statin therapy. Coronary Heart Disease (CHD); Cerebrovascular Disease (CeV D); Peripheral Vascular Disease (PVD); Cardiovascular disease (CVD).

Additionally, we evaluated if increasing number of risk factors for metabolic syndrome would have any effect. The prevalence of CHD, PVD, and total CVD increased with increasing risk factors, however this pattern was not seen for CeV D (table 4). Similarly, risk for CHD, PVD and total CVD increased with increasing risk factors for metabolic
syndrome (figure 1 A, 1B, 1D), reaching significance when ≥ 3 risk factors were present. Patients with zero risk factors had no incidence of PVD so reference point was presence of 1 to 2 risk factors. Again there was no increased risk for CeVD with increasing number of risk factors (figure 1 C).

**Figure 1**: Relative Risk (RR) according to number of risk factors (RFs) for Metabolic Syndrome:

A. Coronary Heart Disease (CHD)

B. Cerebrovascular Disease (CeVD)

C. Peripheral Vascular Disease (PVD)

D. Total Cardiovascular Disease (CVD)

**Discussion**

In the current study among a Dutch population of FH we found that those with metabolic syndrome had higher rates of total CVD, CHD, CeVD and PVD. Also, patients with metabolic syndrome were 1.5 times more likely to develop total CVD after adjustment for established risk factors. Additionally, we separately explored the risk of CHD, PVD and CeVD and found that there was a higher risk of developing CHD and PVD, among FH patients with metabolic syndrome. In contrast, in our population the metabolic syndrome did not seem to cause a higher risk of developing CeVD.
Several studies in recent years have reported that the metabolic syndrome is associated with an increase in CVD (2-15). A recent meta analysis by Ford (16) showed that among patients with metabolic syndrome, random-effect estimates of combined relative risk for cardiovascular disease was 1.65. There is a dearth of data looking at the impact of metabolic syndrome on CVD in the Dutch, and certainly we do not know of any study that has explored the association of metabolic syndrome with risk of CVD in patients with FH. Our results regarding increased risk of CVD are consistent with other studies. The finding that metabolic syndrome still plays a role in FH patients, even in those that are already on statin therapy, underscores the importance of vigorous screening and additional pharmacological modulation of these metabolic factors (28).

There are a few studies that have looked separately into effect of metabolic syndrome on CeVD (9, 12,18, 19). McNeill et al (12) in a recent study showed higher risk for ischemic stroke in women, but not for men. Whereas, some studies (18, 19) have shown higher odds of stroke, Ford (9) did not show a higher risk of stroke mortality due to metabolic syndrome. We considered ischemic stroke or transient ischemic attack as an outcome and also could not demonstrate any higher risk for CeVD due to metabolic syndrome. More studies in larger datasets are warranted to assess this question.

There is paucity of data looking at risk of PVD due presence of metabolic syndrome. Mechanistically, Scuteri et al (29) showed that clustering of at least three of metabolic syndrome components is independently associated with increased intima media thickness and vascular stiffness. One study looking at the prevalence among patients with PVD showed that 58% of these patients had metabolic syndrome (30). Our data show similar results (Table 3). We also showed a higher risk of PVD due to the presence of metabolic syndrome.

In the present study, we defined FH on the basis of strict criteria and applied a meticulous method to data collection to ensure reliable information. In fact, we applied similar methodology as in intervention trials: standardized history and physical examination was documented in a tested case record form; registration was centrally monitored; additional questionnaires were used when data collection was incomplete; and dubious
endpoints were presented anonymously to an independent adjudication committee. In addition, the large size of the cohort allowed analyses of multiple risk factors. Finally, the patients were recruited from all over the country and selection on large families or on genetically isolated populations could be avoided. Nevertheless, our results are derived from patients referred to lipid clinics and therefore caution is required when interpreting the results. Our data may not apply to asymptomatic FH patients in the general population who are undiagnosed. Conversely, patients at the highest risk might have died before visiting a lipid clinic, which might have caused underestimation of our results. However, in mortality analyses we rarely observed such early deaths (31).

In the past there has been contradictory data on overt hypertension and diabetes as risk factors for CVD in FH patients (32-36). We have previously shown that hypertension and diabetes were both independent risk factors for risk of CVD in such a population, the present study is the first of its kind that looks at metabolic syndrome as an entity in patients with FH and shows that it is indeed a risk factor for CVD.

One may suppose a higher risk of CVD due to high LDL levels in this population. However, previously we have shown (20) that LDL cholesterol was not a distinguishing risk factor for CVD in this cohort. This is because of the comparison of patients with high LDL cholesterol to others with similarly high LDL cholesterol. The resulting narrow range of LDL concentrations provides insufficient power to observe an effect from LDL differences. The same phenomenon has been observed in previous studies with FH patients. In studies where two groups of FH patients are compared, LDL cholesterol did not emerge as a risk factor (34, 35), whereas it does emerge as a risk factor in studies in which FH patients are compared with non-FH controls (37). Despite the fact that our comparison consisted of patients with high LDL cholesterol levels we still adjusted for it to minimize any bias.

It has been asserted that establishing how well the metabolic syndrome predicts future adverse health outcomes is a matter of some urgency and especially research in various population subgroups may help in assessing how well the metabolic syndrome predicts risk (16). Our study looked at risk of metabolic syndrome among a large group of
Dutch patients with FH and showed that metabolic syndrome is not only associated with increased total CVD but also with PVD and CHD. However there was no association between metabolic syndrome and risk of CeVD. Future studies in larger datasets are required especially looking at the impact of metabolic syndrome and CeVD and PVD. Moreover, assessing the impact and utility of different therapeutic options for metabolic syndrome in different dyslipidemias remains an important area of future research.

Acknowledgements

This study was supported by a grant from the Netherlands Heart Foundation (98/165). J.J.P. Kastelein is an established investigator of the Netherlands Heart Foundation (grant D039/66510). We acknowledge the members of the independent endpoint committee: Dr R.J.G. Peters, cardiologist, Prof. Dr J. Stam, neurologist and Prof. Dr D. Legemate, vascular surgeon, all from the Academic Medical Centre, Amsterdam, the Netherlands. We thank all the patients who participated and the specialists of the lipid clinics throughout the Netherlands. JW Jukema is an established investigator of the Netherlands Heart Foundation 2001 D032

References


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