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

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Various studies (1–16) in recent years have reported that the metabolic syndrome is associated with an increase in cardiovascular disease (CVD). However, there is still an uncertainty about the clinical importance and consequences of the metabolic syndrome (17). There is paucity of data looking at the effect of metabolic syndrome, specifically on cerebrovascular (CeVD) (9,12,18,19) and peripheral vascular (PVD) disease. Heterozygous familial hypercholesterolemia (FH) is a common hereditary disorder of lipoprotein metabolism (prevalence 1:400). The disorder is caused by mutations in the LDL receptor gene. The objective of our study was to assess if there was an additional risk associated with the presence of metabolic syndrome for coronary disease, CeVD, and PVD in this high-risk population, which included patients inducted from 27 clinics around the Netherlands.

## RESEARCH DESIGN AND METHODS

— The database for the current study is the molecular diagnostic center for nationwide FH screening in the Netherlands, located at the Academic Medical Centre, University of Amsterdam. A total of 2,400 patients fulfilled the diagnostic criteria for FH and were included in the study. The inclusion and exclusion criteria for participation in the study and details of the data collection are outlined and previously discussed in detail (20–22). The ethics institutional review board of each participating hospital approved the protocol.

Metabolic syndrome was defined as per National Cholesterol Education Program Adult Treatment Plan criteria (23), along with the recently suggested modifications (24). We did not have waist circumference information, so we substituted for BMI and based our cut offs on a recent National Health and Nutrition Examination Survey III analysis (25). A diagnosis required the concomitant presence of three or more of the following risk factors: *1*) elevated triglycerides (≥1.7 mmol/l), *2*) low HDL cholesterol (men <1.03 mmol/l; women <1.29 mmol/l), *3*) fasting glucose ≥5.55 mmol/l or medication use for diabetes, *4*) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or medication use for hypertension, and *5*) BMI ≥30 kg/m$^2$ for men and ≥25 kg/m$^2$ for women. Total CVD was defined by the presence of at least one of the following: *1*) coronary heart disease (CHD), *2*) CeVD, or *3*) PVD. The criteria to define each one of these three end points have been explained previously in detail (21).

Differences in clinical characteristics between patients with and without metabolic syndrome were tested with $\chi^2$ statistics or independent sample *t* tests where appropriate. We analyzed the lifetime risk of CVD in these patients. The relative risks (RRs) were estimated from a Cox regression analysis that modeled the lifetime hazard of events; thus, we looked at the risk of CVD events starting at birth and ending 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. We verified any vascular end point that may have occurred before presentation to the vascular lipid clinics. The following variables were entered into the analyses: sex, smoking (time dependent), LDL cholesterol, and 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) and SAS software (Version 8.02; Cary, NC). A *P* value <0.05 was considered to be statistically significant.

## RESULTS

— Of 2,400 patients with FH, we had all five variables to make a diagnosis of metabolic syndrome in 1,698 patients. Of these, metabolic syndrome was present in 31%. Prevalence of overt diabetes was low (5.4% among those with metabolic syndrome and 0.4% among without metabolic syndrome).

A higher number of patients with metabolic syndrome suffered from any CVD (39%) versus those without metabolic syndrome (24%; $P < 0.001$). Table 1 shows that patients with metabolic syndrome were at an increased risk of CHD (RR 1.54 [95% CI 1.23–1.94]) and PVD (1.97 [1.13–3.45]). For CeVD, the results were not significant.

Additionally, we evaluated if increasing the number of risk factors for metabolic syndrome would have any incremental affect. Risk increased with in-

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**Abbreviations:** CeVD, cerebrovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; PVD, peripheral vascular disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Table 1—*Characteristics and RRs by metabolic syndrome status in 1,698 patients with FH***

| | Metabolic syndrome | | |
|---|---|---|---|
| | Absent | Present | *P* value |
| Patient characteristics | | | |
| *n* | 1,041 (69) | 657 (31) | |
| Age (years) | 42 ± 12 | 48 ± 12 | <0.001 |
| Female sex | 508 (49) | 351 (53) | 0.06 |
| BMI (kg/m$^2$) | 24.1 ± 3.0 | 27.1 ± 3.6 | <0.001 |
| Triglycerides (mmol/l) | 1.45 ± 0.75 | 2.43 ± 1.16 | <0.001 |
| HDL cholesterol (mmol/l) | 1.30 ± 0.35 | 1.04 ± 0.27 | <0.001 |
| Fasting glucose (mmol/l) | 4.82 ± 0.65 | 5.45 ± 1.24 | <0.001 |
| Systolic blood pressure (mmHg) | 130 ± 17 | 142 ± 19 | <0.001 |
| Diastolic blood pressure (mmHg) | 80 ± 10 | 86 ± 10 | <0.001 |
| LDL cholesterol (mmol/l) | 7.2 ± 1.9 | 7.4 ± 1.9 | 0.064 |
| Diabetes | 4 (0.4) | 35 (5.4) | <0.001 |
| Current smoking | 326 (32) | 230 (36) | 0.08 |
| Family history of myocardial infarction | 561 (54) | 362 (55) | 0.63 |
| Statin therapy | 304 (29) | 252 (38) | <0.001 |
| RRs* | | | |
| CHD | 209 (20); reference | 225 (34); 1.54 (1.23–1.94) | <0.001 |
| CeVD | 26 (2.5); reference | 29 (4.4); 1.64 (0.88–3.05) | 0.12 |
| PVD | 30 (2.9); reference | 41 (6.2); 1.97 (1.13–3.45) | 0.017 |
| Total CVD | 245 (24); reference | 256 (39); 1.50 (1.21–1.85) | <0.001 |

Data are means ± SD, *n* (%), or RR (95% CI). *Adjusted for sex, smoking, LDL cholesterol, and statin therapy.

creasing risk factors for metabolic syndrome for CHD (one to two risk factors: RR 1.65 [95% CI 0.93–2.92] and three or more risk factors: 2.42 [1.37–4.29]) and total CVD (one to two risk factors: 1.60 [0.96–2.68] and three or more risk factors: 2.29 [1.36–3.83]). Patients with zero risk factors had no incidence of PVD, and therefore the reference point was the presence of less than three risk factors (three or more risk factors: 1.72 [0.99–3.02]). Again, there was no significant increased risk for CeVD with increasing number of risk factors (one to two risk factors: 0.83 [0.24–2.88] and three or more risk factors: 1.40 [0.41–4.84]).

**CONCLUSIONS** — Among a Dutch population of FH, we found that those with metabolic syndrome were 1.5 times more likely to develop total CVD after adjustment for established risk factors. Additionally, we separately explored and found that there was a higher risk of developing CHD and PVD among FH patients with metabolic syndrome.

Our results regarding increased risk of CVD are consistent with other studies (16). The finding that metabolic syndrome plays a role in determining risk 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 (27).

There are limitations to our study. Our results are derived from patients referred to lipid clinics, and therefore caution is required when interpreting the results. 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 (28).

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 a risk factor for total CVD, along with CHD and PVD. The impact and utility of different therapeutic options for metabolic syndrome in different dyslipidemias remains an important area of future research.

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