

File ID 228530
Filename Chapter 8: Metabolic dyslipidemia and risk of future coronary heart disease in apparently healthy men and women: the EPICNorfolk prospective population study

SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type Dissertation
Title Dyslipidemia, sense, antisense or nonsense?
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Faculty Faculty of Medicine
Year 2011
Pages 194
ISBN 9789461081940

FULL BIBLIOGRAPHIC DETAILS:

<http://dare.uva.nl/record/391041>

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International Journal of Cardiology 2010;143:399–404

Chapter

8

Metabolic dyslipidemia and risk of future coronary heart disease in apparently healthy men and women: The EPIC-Norfolk prospective population study

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Abstract

Background

The association of metabolic syndrome and risk of CHD is now well established. The association between 'metabolic dyslipidemia' as defined by high triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-c) levels and the risk of coronary heart disease (CHD) risk is not known. The aim of this study was to investigate the association between metabolic dyslipidemia, and risk of CHD in apparently healthy men and women.

Methods

Metabolic dyslipidemia was defined by combination of increased TG levels (≥ 150 mg/dl) and low HDL-c levels (≤ 50 mg/dL for women and ≤ 40 mg/dL for men). In the EPIC-Norfolk prospective population study, 21,340 participants without diabetes (9326 men and 12,014 women) were followed for a mean of 11.4 years during which 2075 CHD events occurred. Three multivariate models were used adjusting for other metabolic risk factors including low-density lipoprotein cholesterol (LDL-c).

Results

Compared to men with normal HDL-c and normal TG, men with metabolic dyslipidemia had an increased risk for CHD (HR: 1.61; 95% CI: 1.40-1.86). The increased risk remained significant after adjustment for LDL-c and other metabolic risk factors. Among women, metabolic dyslipidemia was associated with increased CHD risk (HR: 1.78; 95% CI: 1.47-2.15). This association was lost when the model was additionally adjusted for other metabolic syndrome risk factors. In men and women Kaplan-Meier survival curves according to HDL-c and TG levels revealed that participants with metabolic dyslipidemia had poorer survival compared to people without metabolic dyslipidemia (logrank < 0.001 for each).

Conclusion

Metabolic dyslipidemia is associated with an increased risk of CHD. This relationship was independent from LDL-c and other risk factors of the metabolic syndrome in men, but not in women. A better management of this phenotype via lifestyle modification or pharmacotherapy may be warranted.

Introduction

Type 2 diabetes mellitus and the metabolic syndrome are associated with an atherogenic lipoprotein-lipid profile characterized by hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c) and a preponderance of small-dense, low-density lipoprotein (LDL) particles. This particular lipid profile is often referred to as the atherogenic triad or atherogenic dyslipidemia¹. However, since other dyslipidemias are also atherogenic², we shall refer to this abnormal lipid pattern prevalent in patients with metabolic disorders as 'metabolic dyslipidemia'. Studies have reported that the relationship between small-dense LDL particles and CHD risk largely depends on the presence of the metabolic dyslipidemia^{3,4}. High triglycerides (TG) (TG ≥ 150 mg/dL or ≥ 1.69 mmol/L) and low HDL-c (≤ 50 mg/dL or ≤ 1.0 mmol/L for women and ≤ 40 mg/dL or ≤ 0.9 mmol/L for men) represent two of the five risk factors of the metabolic syndrome⁵. Although the risk of CHD associated with either high TG levels or low HDL-c levels have been evaluated extensively^{6,7}, the risk associated with the combination of low HDL-c and high TG levels remains largely unknown. We therefore sought to evaluate the risk of CHD associated with metabolic dyslipidemia, defined as low levels of HDL-c and high TG levels in men and women enrolled in the EPIC-Norfolk prospective population study, a cohort representative of a contemporary Western population.

Methods

Study population

EPIC-Norfolk is a prospective population study of 25,663 men and women aged 45 to 79 years residing in Norfolk, United Kingdom, who completed a baseline questionnaire survey and attended a clinic visit⁸. Participants were recruited from age and sex registers of general practices in Norfolk as part of the 10-country collaborative EPIC, which was designed to investigate dietary and other determinants of cancer. Additional data were obtained in EPIC-Norfolk so that determinants of other diseases such as CHD could also be assessed. The design and methods of EPIC-Norfolk are described in detail elsewhere⁸. In short, eligible participants were recruited by mail. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire. All participants were flagged for death certification at the United Kingdom Office of National Statistics, and vital status was ascertained for the entire cohort. In addition, hospitalized participants were identified by using their unique National Health Service number through data linkage with the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. CHD was defined

as codes 410 to 414 of the International Classification of Diseases, Ninth Revision. Participants were identified as having CHD during follow-up if they had a hospital admission or died with CHD as an underlying cause. Previous validation studies in our cohort indicate high specificity for such case ascertainment⁹. The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent.

Follow-up and outcome events

We excluded all participants who reported a history of heart attack or stroke or use of lipid-lowering drugs at the baseline clinic visit. Cases were participants who developed fatal or nonfatal CHD during follow-up through 31 March 2007, an average of 10.9 years. Controls were study participants who remained free of any cardiovascular disease during follow-up. Whenever possible, 2 controls were matched to each case by age (within 5 years), sex, and time of enrollment period (within 3 months). At the baseline survey, participants completed a detailed health and lifestyle questionnaire, and additional data collection was performed by trained nurses at a clinic visit. Habitual physical activity was assessed using two questions referring to activity during the past year. The first question asked about physical activity at work, the second about the amount of time spent in hours per week in activities: cycling and leisure time physical activities such as jogging or swimming, in winter and summer separately. A simple physical activity index was devised to allocate individuals to four categories of usual increasing physical activity: inactive, moderately inactive, moderately active and active. This index was validated against heart rate monitoring in 173 individuals over 1 year¹⁰.

Biochemical analyses

Serum concentrations of total cholesterol, HDL-c, and TG were measured in fresh serum samples with the RA1000 (Bayer Diagnostics, Basingstoke, UK), and LDL cholesterol (LDL-c) concentrations were calculated with the Friedewald formula¹¹. Samples were analyzed in random order to avoid systemic bias. Researchers and laboratory personnel had no access to identifiable information, and could identify samples by number only. HbA1c measurements were performed in approximately half the cohort when funding became available as described previously¹².

Statistical analyses

For the present analysis, we excluded all participants with known diabetes mellitus and prevalent CHD. Subjects were divided into four different groups according to triglyceride and HDL-c levels. For TG levels, the cut-off value was 150 mg/dL for both men and women and for HDL-c the cut-off value was 50 mg/dL for men

and 40 mg/dL for women, as suggested by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII). Values below these cut-off values were considered 'normal' for TGs and 'low' for HDL-c. Values higher than these cut-off values were considered 'high' for TGs and 'normal' for HDL-c. Differences between baseline characteristics of subjects within each group were analyzed using ANOVA. To estimate the relationship between metabolic dyslipidemia and CHD risk, hazard ratios (HR) and associated 95% confidence intervals (95%CI) were calculated using a Cox proportional hazard model. The group with normal TG and HDL-c was used as reference. Four different models were used. Model 1 adjusted for physical activity, age, smoking (never, past, current) and hormone therapy (women only). Model 2 additionally adjusted for LDL-c. Model 3 additionally adjusted for waist circumference, systolic blood pressure. Model 4 additionally adjusted for HbA1c; HbA1c was not available for the full cohort. Kaplan-Meier survival curves according to TG and HDL-c levels were assessed in men and women of the entire cohort. Statistical analyses were performed by using SPSS software, version 10.0 (SPSS, Inc, Chicago, Illinois).

Results

Out of the 21,240 participants (9226 men and 12,014 women) without CHD and diabetes at baseline, 2075 experienced CHD events during followup (1307 men and 768 women). As expected, most baseline characteristics differed significantly between the four groups (table 1). Only age was comparable between the four groups among men. Participants with metabolic dyslipidemia were more likely to smoke and to have higher adiposity indices such as BMI and waist circumference as well as an increased systolic and diastolic blood pressure ($p < 0.001$ for each). While total cholesterol levels were increased in participants carrying the metabolic dyslipidemia, only women with metabolic dyslipidemia were more likely to have higher LDL-c and HbA1c levels compared to women classified on the basis of other lipid combinations. Participants with metabolic dyslipidemia had an increased risk of future CHD (HR=1.61; 95%CI: 1.40-1.86 for men and HR=1.78; 95% CI: 1.47-2.15 for women) when compared to the reference group (table 2). This risk remained significantly elevated upon adjustment for LDL-c (model 2) and additional adjustment for the systolic blood pressure and waist circumference (model 3). Among men, presence of the metabolic dyslipidemia was still associated with 50% increased risk for CHD even after adjustment for HbA1c (model 4). We also found that men with either high or normal TG levels were at increased CHD risk if they had low HDL-c levels, even in the multivariate analyses. Among women, although metabolic dyslipidemia was associated with

Table 1 Characteristics of 21,240 participants of EPIC Norfolk Cohort

HDL cholesterol levels	Normal/	Normal/	Low/	Low/	P-value
Triglyceride levels	Normal	High	Normal	High	
Men (n = 9226)	4014	2385	929	1998	
Age, y	59 ± 9	59 ± 9	59 ± 10	59 ± 9	0.08
BMI, kg/m ²	25.5 ± 2.9	26.8 ± 3.1	26.5 ± 3.2	27.6 ± 3.2	< 0.001
Waist circumference, cm	92 ± 9	97 ± 9	96 ± 9	99 ± 9	< 0.001
Smoking, % - Current	11.4	10.7	14.7	14.1	< 0.001
- Past	51.1	58.4	49.3	53.1	
- Never	37.5	30.9	36.0	32.9	
Systolic blood pressure, mmHg	135 ± 17	139 ± 17	135 ± 18	138 ± 17	< 0.001
Diastolic blood pressure, mmHg	83 ± 11	86 ± 11	83 ± 11	85 ± 11	< 0.001
Total cholesterol, mmol/L	5.8 ± 1.0	6.5 ± 1.1	5.3 ± 1.0	6.1 ± 1.0	< 0.001
LDL-c, mmol/L	3.8 ± 0.9	4.1 ± 1.0	3.8 ± 0.9	4.0 ± 1.0	< 0.001
HDL-c, mmol/L	1.4 ± 0.3	1.3 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	< 0.001
Triglycerides, mmol/L	1.2 (0.9-1.4)	2.3 (2.0-2.7)	1.4 (1.1-1.6)	2.6 (2.1-3.2)	< 0.001
HbA1c, %	5.2 ± 0.6	5.3 ± 0.8	5.2 ± 0.6	5.3 ± 0.7	< 0.001
Women, n= 12,014	7027	2211	1247	1529	
Age, y	57 ± 9	62 ± 9	56 ± 9	61 ± 9	< 0.001
BMI, kg/m ²	25.1 ± 3.6	27.3 ± 4.3	26.7 ± 4.5	28.5 ± 4.5	< 0.001
Waist circumference, cm	79 ± 9	85 ± 10	83 ± 11	89 ± 11	< 0.001
Smoking, % - Current	10.2	10.6	13.7	15.4	< 0.001
- Past	32.1	33.9	28.8	29.4	
- Never	57.7	55.4	57.5	55.1	
Systolic blood pressure, mmHg	131 ± 18	139 ± 18	130 ± 17	139 ± 19	< 0.001
Diastolic blood pressure, mmHg	79 ± 11	84 ± 11	79 ± 11	84 ± 11	< 0.001
Total cholesterol, mmol/L	6.1 ± 1.1	7.0 ± 1.1	5.7 ± 1.1	6.7 ± 1.2	< 0.001
LDL-c, mmol/L	3.8 ± 1.0	4.3 ± 1.1	4.0 ± 1.1	4.5 ± 1.1	< 0.001
HDL-c, mmol/L	1.8 ± 0.4	1.6 ± 0.3	1.1 ± 0.1	1.1 ± 0.1	< 0.001
Triglycerides, mmol/L	1.1 (0.8-1.4)	2.2 (1.9-2.6)	1.3 (1.0-1.5)	2.5 (2.1-3.0)	< 0.001
HbA1c, %	5.1 ± 0.6	5.4 ± 0.8	5.1 ± 0.7	5.5 ± 0.9	< 0.001

Data are presented as mean ± SD, percentage (number) or median (interquartile range).

an increased CHD risk, women with high TG and normal HDL-c and women with normal TG and low HDL-c levels were also found to be at increased risk. In fact women of these subgroups were at increased risk even after adjustment for model 4 whereas women carrying the metabolic dyslipidemia were found to be at increased risk after adjustment for model 3, but not after adjustment for model 4. Finally, Kaplan-Meier survival curves according to TG and HDL-c levels were assessed in the entire cohort. Figure 1 shows that participants carrying metabolic dyslipidemia had poorer survival than participants with normal triglyceride and HDL-c levels.

Table 2 Risk of future coronary heart disease (CHD) among men and women

HDL cholesterol levels	Normal	Normal	Low	Low
Triglyceride levels	Normal	High	Normal	High
Men CHD Events (n= 1307)	443	361	153	350
HR for future CHD ¹	1.0	1.35 (1.17-1.55)	1.50 (1.24-1.80)	1.61 (1.40-1.86)
HR for future CHD ²	1.0	1.24 (1.08-1.43)	1.54 (1.28-1.85)	1.56 (1.36-1.80)
HR for future CHD ³	1.0	1.15 (1.00-1.32)	1.49 (1.23-1.79)	1.43 (1.24-1.66)
*HR for future CHD ⁴ Cases/ controls	168/1694 1.0	152/985 1.18 (0.95-1.48)	59/331 1.67 (1.24-2.25)	139/769 1.50 (1.19-1.90)
Women CHD Events (n= 768)	320	212	74	162
HR for future CHD ¹	1.0	1.50 (1.26-1.79)	1.54 (1.20-1.99)	1.78 (1.47-2.15)
HR for future CHD ²	1.0	1.43 (1.20-1.71)	1.49 (1.16-1.93)	1.66 (1.37-2.02)
HR for future CHD ³	1.0	1.31 (1.09-1.56)	1.42 (1.10-1.83)	1.42 (1.16-1.74)
*HR for future CHD ⁴ Cases/ controls	123/3246 1.0	91/940 1.43 (1.08-1.90)	27/522 1.57 (1.03-2.40)	52/601 1.32 (0.93-1.86)

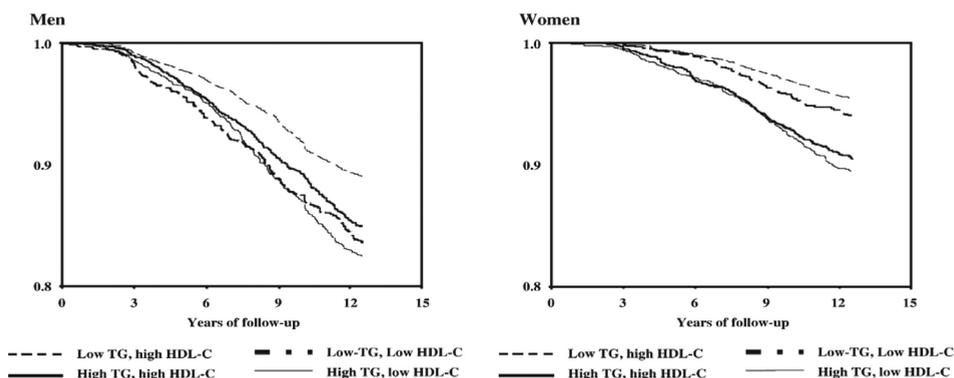
Hazard Ratio (95% CI)

Model 1 adjusted for age, smoking (never, past, current) and hormone therapy (women only) and activity.

Model 2 additionally adjusted for low-density lipoprotein cholesterol (LDL-c).

Model 3 additionally adjusted for waist circumference, systolic blood pressure.

*Model 4 additionally adjusted for HbA1c; HbA1c was not available for the full cohort.

Figure 1 Kaplan-Meier survival curves according to TG and HDL-c levels

Discussion

In this prospective cohort study, we observed that metabolic dyslipidemia (low HDL-c and high TG) was a CHD risk factor in both men and women. Even after adjustment for LDL-c the risk of CHD in participants with the metabolic dyslipidemia, remained elevated. Among men, the metabolic dyslipidemia was

still associated with an elevated CHD risk after controlling for other risk factors associated with the metabolic syndrome. In women, the association between metabolic dyslipidemia and elevated CHD risk remained statistically significant after adjustment for potential confounders such as LDL-c, waist circumference and systolic blood pressure, but not after further adjustment for HbA1c.

Our observation that metabolic dyslipidemia is an independent risk factor for CHD even beyond LDL-c is consistent with a recently published study showing that the presence of low HDL-c and high TG was an independent predictor of CHD in a relatively small population of patients with known CHD (n=284)¹³. That study however included patients with diabetes, did not compare four categories defined by both TG and HDL-c levels and did not control for waist circumference and blood pressure. A post-hoc analysis of the Scandinavian Simvastatin Survival Study showed that patients with the lipid triad of elevated levels of LDL-c, low levels of HDL-c and high levels of TG had an increased risk for CHD events compared to patients with isolated LDL-c elevation¹⁴.

The large number of participants enrolled in this study enabled us to look into the sex-specific combinations of TG and HDL-c levels. In men, we found that participants with low HDL-c with high or normal TG levels had virtually the same odds of eventually developing CHD. We also observed that TG levels were not predictive of CHD in men with normal HDL-c. These observations clearly highlight the role of low HDL-c levels as an important CHD risk factor, independently from all other markers of atherogenic dyslipidemia/metabolic syndrome. Although we found that women carrying the metabolic dyslipidemia had a CHD risk that was slightly higher than men in univariate analyses, the relationship between metabolic dyslipidemia and CHD risk appeared to be more dependent on underlying risk factors such as HbA1c levels. In fact, in the final model of adjustment, women with metabolic dyslipidemia were not found to be at increased risk whereas women with high TG and normal HDL-c levels and women with normal TG and low HDL-c levels were at increased risk. Based on these observations, the cardioprotective role of HDL-c was observed in both men and women whereas high TG levels, without low HDL-c levels, were predictive of CHD only in women. The reasons for these unexpected findings in women need to be validated in other population studies. These results are consistent with the hypothesis that risk factors of CHD are interdependent in the metabolic syndrome and that the metabolic syndrome might confer cardiovascular risk beyond what can be explained by its individual components¹⁵.

A number of aspects of our study warrant further discussion. Strengths of our study include the large number of participants and the fact that follow-up was long. It is also important to note that participants were recruited from an unrestricted and homogeneous population. We excluded people who had previously experienced myocardial infarction or stroke or documented diabetes, thus limiting the impact of such events on the relationship of metabolic dyslipidemia and CHD risk. A potential limitation of the present study remains in the fact that biochemical analyses were performed in nonfasting serum samples that were obtained at a non-uniform time of the day. Therefore, we did not measure blood glucose and used HbA1c, which levels do not vary in the postprandial state, as a surrogate marker of fasting glucose. HbA1c levels were only available for 50% of the subjects, which resulted in a substantial loss of statistical power when HbA1c was used in regression analyses (model 4). The non-uniform time of blood sampling might also have affected serum TG levels. Indeed a study has shown that fasting TG was associated with increased risk of CHD in men¹⁶. While other large scale cohorts have shown that nonfasting TG was also a risk factor for CHD for both women¹⁷ and men¹⁸. We were unable to adjust for diet variables since they were not available for every participant in the cohort. However, our simultaneous adjustment for physical activity and waist circumference may cover the majority of confounding introduced by dietary variables.

In conclusion, in men and women of this cohort representative of a contemporary Western population, we found that, metabolic dyslipidemia is a predictor of CHD independent from LDL-c. The relationship between metabolic dyslipidemia and CHD risk was independent from the other risk factors associated with the metabolic syndrome in men, but not in women. Based on the results of the present study, a better management of this phenotype via lifestyle modification or pharmacotherapy may be warranted in order to lower the risk associated with this atherogenic phenotype. On similar lines the Residual Risk Reduction Initiative was recently introduced to address this highly relevant clinical issue¹⁹.

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