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Dyslipidaemia as a predictor of hypertension in middle-aged men

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Aims Dyslipidaemia and hypertension are features of the metabolic syndrome, but the role of dyslipidaemia in the development of hypertension is less clear. We assessed the association of dyslipidaemia with incident hypertension during a 7-year follow-up in a population-based cohort of middle-aged men without hypertension at baseline.

Methods and results In all, 88 of 311 men developed hypertension during the follow-up. A 1-SD increment in triglyceride concentrations was associated with a 1.6-fold [95% CI(confidence interval) 1.2–2.3] increased risk of developing hypertension, independently of features related to the metabolic syndrome. In separate multivariable models, the triglyceride content of high-density lipoprotein (HDL) cholesterol and apolipoprotein B concentrations were also associated with new-onset hypertension. In a stepwise backwards logistic regression model, concentrations of low-density lipoprotein (LDL) cholesterol [odds ratio (OR) 1.3, 95% CI 1.0–1.7 for a 1-SD change] and triglyceride content of HDL cholesterol (OR 1.5, 95% CI 1.1–1.9) were positively associated with incident hypertension, whereas HDL concentrations (OR 0.7, 95% CI 0.5–0.9) seemed protective. In factor analyses, elevated triglyceride levels and related disturbances in lipid and cholesterol metabolism were associated with new-onset hypertension.

Conclusion Dyslipidaemia characteristic of the metabolic syndrome predicts the development of hypertension during a 7-year follow-up of eastern Finnish men, independently of features related to insulin resistance. The recognition of dyslipidaemia and initiation of lifestyle treatment even in the absence of hypertension is likely to reduce the long-term burden of cardiovascular disease.

Keywords Hypertension • Lipoproteins • Apolipoproteins • Triglycerides • Lipoprotein triglycerides • Cohort studies

Introduction

Hypertension and dyslipidaemia are well-established and partially overlapping risk factors for cardiovascular disease.[1–6] Moreover, hypertension and dyslipidaemia are manifestations of the metabolic syndrome, which is also a consequence of the interaction of genes and the environment.[1,7,8] The pathogenesis of hypertension and the metabolic syndrome is only partly understood, but endothelial dysfunction likely plays a role in both.[9,10]

In the Physicians' Health Study, total cholesterol, non-high-density lipoprotein (HDL)-cholesterol and HDL-cholesterol predicted onset of hypertension in 3110 men without self-reported hypertension.[11] These findings agree with some of the few prospective studies on dyslipidaemia and incident hypertension.[12–14] Thus, hypertension may be a consequence of dyslipidaemia or closely related metabolic abnormalities. None of these studies has adjusted extensively for features of the metabolic syndrome. Little is known of the association between other features of dyslipidaemia, such as apolipoprotein A, apolipoprotein B, or triglyceride content of the low-density lipoprotein (LDL) or HDL particles, and incident hypertension.

Elevated triglyceride-rich lipoproteins, VLDL, small dense LDL particles and apolipoprotein B and low HDL cholesterol and apolipoprotein A are characteristic features of dyslipidaemia in the metabolic syndrome and type 2 diabetes.[15] In addition to reverse cholesterol transport, HDL cholesterol stimulates nitric

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oxide (NO) production, inhibits adhesion of monocytes to endothelium, and has antithrombotic and antioxidant effects.[16] In contrast, LDL cholesterol and triglycerides may damage the epithelium, impair NO release and cause endothelial dysfunction.[17] Therefore, dyslipidaemia could cause hypertension by mechanisms only partly related to obesity and insulin resistance.

We hypothesized that dyslipidaemia would predict incident hypertension during a 7-year follow-up of 311 middle-aged Finnish men participating in a population-based study. In addition to commonly measured lipid and lipoprotein fractions, we also measured the triglyceride content of LDL and HDL cholesterol and apolipoproteins A and B. Because the various measures of dyslipidaemia are intercorrelated, we used factor analysis as a complementary analytic approach to logistic regression to provide further insight into the association of dyslipidaemia with the development of hypertension.

Methods

Study population

The subjects were participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD).[18] Participants were a random age-stratified sample of men living in Eastern Finland who were 49, 55, 61 or 67 years old at the baseline examination of this study in 1991–1994. The recruitment and study design have previously been described in detail.[18] Repeat examinations were carried out in 1998–2001. In all, 1038 participated in the baseline examinations, and 854 men (90% of those alive) participated in the 7-year follow-up. Men with hypertension at baseline were excluded, leaving 311 men for analyses of incident hypertension during the 7-year follow-up. The participants were examined in the same month as at baseline 7 years later. This was not possible for many, but follow-up was within 3 months of 7 years for 75% of the men. The median length of follow-up was 6.99 years (interquartile range 7.74–7.25 years). None used cholesterol-lowering medication at baseline. The study was carried out in accordance with the Declaration of Helsinki and was approved by the university ethics committee. All participants gave their written informed consent.

Definition of hypertension

Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley & Sons, Lancing, UK). The protocol included three measurements while supine, one while standing and two while sitting, with 5-min intervals between measurements. The mean of the two measurements while sitting was used as the blood pressure. Hypertension was defined at baseline and follow-up as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or current use of antihypertensive medication.[19,20]

Lipoprotein, apolipoprotein, and lipid measurements

HDL cholesterol was separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically. The triglyceride concentrations of HDL and LDL cholesterol were similarly determined after isolation of HDL and LDL cholesterol. Analyses of apolipoprotein A1 and apolipoprotein B were based on the measurement of immunoprecipitation enhanced by polyethylene glycol (PEG) at 340 nm[21] using a Kone Specific Chemical Analyzer (Kone Ltd., Espoo, Finland).

Anthropometric and biochemical measurements

Body mass index was computed as the ratio of weight to the square of height (kg/m^2). Waist circumference was defined as the average of two measurements taken at the midpoint between the lowest rib and the iliac crest after inspiration and expiration.

Fasting blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Diabetes was defined as fasting blood glucose concentration $\geq$6.1 mmol/L (equivalent to plasma glucose $\geq$7.0 mmol/L) or a clinical diagnosis of diabetes with dietary, oral or insulin treatment.[22] Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). Fibrinogen was measured based on the clotting of diluted plasma with excess thrombin. Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, CA, USA).[23]

Other assessments

The assessments of medical history and medications, smoking, alcohol consumption, adult socioeconomic status and leisure-time physical activity have been described previously.[24,25] Dietary intake of saturated fat, sodium, potassium and fruits and vegetables were measured with 4-day food records as g/d and adjusted by regression analysis for energy intake.[26] High-resolution B-mode ultrasonography was used to examine a 1.0–1.5-cm section at the distal end of the left and right common carotid artery proximal to the carotid bulb, as explained in detail elsewhere.[27]

Statistical analyses

Differences in baseline characteristics between men who developed hypertension and those who did not were assessed with Student's *t*-test, and where indicated, the χ^2 test. To investigate the associations of the concentrations of individual lipids, lipoproteins and apolipoproteins with incident hypertension, we carried out logistic regression analyses with adjustment according to the following models: model 1, adjusted for age; model 2, adjusted for age and systolic blood pressure at baseline; model 3, adjusted for age, smoking (never-smoker, former smoker, and current smoker), alcohol intake (g/week), adult socioeconomic status, leisure-time physical activity, presence of cardiovascular disease, and presence of diabetes; model 4, adjusted for the variables in model 3 and waist girth, concentrations of insulin, glucose and C-reactive protein, maximal carotid intima media thickness and baseline systolic blood pressure. The variables in question were entered into logistic regression models adjusting for age and potential mediating or confounding variables. The linearity of the association of the lipid, lipoprotein, and apolipoprotein variables was assessed by categorization of the variables into thirds. The association of lipid variables appeared linear, except for triglyceride concentrations in which the middle and upper third of the concentrations were similarly associated with a higher risk of hypertension. Therefore all lipid, lipoprotein, and apolipoprotein variables were analysed using continuous variables. The covariates for the logistic regression models were forced into the model. In analyses with all of the lipids, lipoproteins, and apolipoproteins expressed as continuous variables, stepwise backward logistic regression was used. As a complementary approach for assessing the associations of dyslipidaemia with incident hypertension, factor analysis was carried out using lipid, lipoprotein, and apolipoprotein variables. Principal component analysis was used for

the extraction of the initial factors. Only factors with eigenvalues > 1.0 were retained in the analysis. The initial factors were then rotated. We present analyses using a varimax rotation, and alternatively, a promax rotation to assess possible underlying pathophysiological relationships.[28–30] The varimax rotation generates uncorrelated factors. Uncorrelated factors may simplify interpretation of the factors, but may not be biologically relevant. Therefore, we also carried out a promax rotation to generate correlated factors. The promax rotation allows derivation of correlated factors, which can then be rotated in a second-order factor analysis.[28] The factors were then interpreted as such, but also subjected to a second-order factor analysis. Cut-offs for loading varying from 0.20 to 0.40 have been recommended for the interpretation of factors.[31,32] For interpretation in this study, we considered variables with loadings ≥ 0.40 to be heavily loaded on the factor, and variables having a correlation coefficient of 0.30–0.39 to be moderately loaded. In analyses using continuous variables, skewed variables were log transformed, except for HDL triglycerides, in which the square root was taken. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 11.0 for Windows (Chicago, IL, USA).

Results

Baseline characteristics

The 88 men who developed hypertension during the 7-year follow-up had higher blood pressure already at baseline (*Table 1*). They more frequently had the metabolic syndrome and more pronounced characteristics related to insulin resistance. Men who became hypertensive during the follow-up were also more dyslipidaemic, except with respect to apoA1 and LDL cholesterol concentrations.

Baseline correlations

Most of the lipids, lipoproteins and apolipoproteins were moderately or strongly intercorrelated (*Table 2*). Especially lipid and apolipoprotein B concentrations were associated with fasting insulin concentrations, waist circumference, and to a lesser extent, systolic blood pressure.

Lipoprotein, apolipoprotein and lipid concentrations, and incident hypertension

In analyses of individual lipids, lipoproteins, and apolipoproteins, a 1-SD increment in serum concentrations of triglycerides was associated with a 1.8-fold higher risk of incident hypertension, even after extensive adjustment for other potential mediating or confounding variables (*Table 3*). Similarly, 1-SD increments in the concentrations of apolipoprotein B and HDL triglycerides were associated with a 1.4–1.6 times higher risk of developing hypertension. LDL cholesterol and LDL triglycerides also predicted the development of hypertension, but the association did not reach significance in the fully adjusted model.

The sample size in our study is rather small for stratified analyses. The associations of the measures of dyslipidaemia were nonetheless similar in men with systolic blood pressure below the median (122 mm HG: for a 1-SD change of triglycerides, OR(odds ratios) = 1.49, 95% CI 1.01–2.19; for HDL triglyceride, OR = 1.68, 95% CI 1.09–2.58; for apolipoprotein B, OR = 1.52, 95% 1.10–2.12) or above the median (for a 1-SD change of triglycerides, OR = 1.97, 95% CI 1.35–2.89; for HDL triglyceride, OR = 1.56, 95% CI 1.09–2.58; for apolipoprotein B, OR = 1.31, 95% 0.91–1.88). The associations seemed to be slightly stronger for men without cardiovascular disease (CVD) at baseline (n = 238: for a 1-SD change of triglycerides, OR = 1.79, 95% CI 1.34–2.39; for HDL triglyceride, OR = 1.73, 95% CI 1.26–2.38; for apolipoprotein B, OR = 1.68, 95% 1.23–2.29) than for those with CVD (n = 73: for a 1-SD change of triglycerides, OR = 1.44, 95% CI 0.88–2.33; for HDL triglyceride, OR = 1.44, 95% CI 0.88–2.34; for apolipoprotein B, OR = 1.44, 95% 0.88–2.33). The interaction of measures of dyslipidaemia and CVD at baseline with respect to incident hypertension was not significant (P = 0.14–0.87), however.

Although somewhat unreliable because of the high collinearity of lipids, lipoproteins and apolipoproteins, we also used stepwise backward multiple logistic regression with age and all the lipid, lipoprotein and apolipoprotein variables as given in *Table 3* as continuous explanatory variables. LDL cholesterol, HDL cholesterol and HDL triglyceride content were significant determinants of incident hypertension in these analyses (*Table 4*).

Factor analysis

To derive uncorrelated factors, we carried out factor analysis of all the lipid, lipoprotein, and apolipoprotein variables as shown in *Table 3* by extracting factors with an eigenvalue ≥ 1 and carrying out a varimax rotation. Three factors were obtained. The factor explaining the greatest variance, 46.5%, was termed the triglyceride factor because of the high loadings of variables related to triglyceride metabolism (*Table 2*). The second factor, which explained 25.1% of the variance, was termed the HDL factor because of the high loading of apolipoprotein A1 and HDL cholesterol. The final factor explaining 15.8% of the variance was termed the LDL factor.

Because uncorrelated factors may not be biologically realistic,[28] we also repeated analyses using a promax rotation. The same three factors with the same variance were obtained, but the loadings on the factors differed slightly from the varimax rotation (*Table 2*). With the promax rotation, the triglyceride factor correlated with the HDL factor ($r = -0.24$) and LDL factor ($r = 0.45$). The HDL and LDL factors were also weakly correlated ($r = -0.16$).

A second-order factor analysis of the factors derived using the promax rotation was carried out. A single factor explaining 52.9% of the variance was derived. This second-order dyslipidaemia factor was loaded onto by the triglyceride factor (0.82), LDL factor (0.78) and HDL factor (−0.55). The dyslipidaemia factor had modest to heavy loadings by all the lipids, lipoproteins, and apolipoproteins (*Table 2*).

Lipid, lipoprotein, and apolipoprotein factors in the prediction of hypertension

Of the factors derived using a varimax rotation, only the triglyceride factor was a significant determinant of incident hypertension (*Table 5*). The LDL factor tended to be associated with incident hypertension in models 1–3.

Table 1 Baseline characteristics of men who developed hypertension during the 7-year follow-up and those who did not

	Non-hypertensive at follow-up	Hypertensive at follow-up	*P*-value
n	223	88	
Age (years)	54.1 (6.7)	55.2 (6.6)	0.12
Smokers			0.21
Never	83, 37%	25, 28%	
Former	79, 35%	31, 35%	
Current	61, 27%	32, 36%	
Alcohol consumption (g/week)	38 (8, 88)	37 (6, 101)	0.67
Cardiovascular disease (*n*, %)	65, 29%	28, 32%	0.70
Diabetes mellitus (*n*, %)	9, 4%	5, 6%	0.53
Maximum carotid IMT (mm)	0.91 (0.80, 1.05)	09 (1.01, 1.21)	0.005
Adult socioeconomic status score	7.0 (4.1)	7.3 (4.0)	0.56
Systolic blood pressure (mmHg)	120 (10)	124 (8)	<0.001
Diastolic blood pressure (mmHg)	79 (7)	81 (6)	0.004
Body mass index (kg/m^2)	25.1 (2.7)	26.1 (2.9)	0.018
Waist circumference (cm)	89.5 (8.9)	92.9 (7.9)	0.002
Fasting blood glucose (mmol/L)	4.48 (0.45)	4.52 (0.47)	0.53
Fasting serum insulin (mIU/L)	4.5 (2.0, 6.5)	8.9 (7.0, 11.2)	<0.001
Fibrinogen (g/L)	3.03 (0.54)	3.20 (0.62)	0.054
C-reactive protein (mg/L)	1.07 (0.57, 2.18)	1.64 (0.74, 3.35)	0.022
Metabolic syndrome, NCEP (*n*, %)	18, 8%	15, 17%	0.015
Moderate and vigorous LTPA (min/week)	162 (81, 305)	128 (56, 241)	0.79
Serum LDL cholesterol (mmol/L)	3.8 (0.9)	4.0 (1.1)	0.067
Serum HDL cholesterol (mmol/L)	1.40 (0.29)	1.28 (0.26)	0.001
Serum triglycerides (mmol/L)	0.96 (0.75, 1.38)	1.21 (1.02, 1.81)	<0.001
Serum LDL triglycerides (mmol/L)	0.30 (0.24, 0.39)	0.37 (0.29, 0.41)	0.002
Serum HDL triglycerides (mmol/L)	0.19 (0.15, 0.22)	0.22 (0.18, 0.25)	<0.001
Serum apolipoprotein B (g/L)	0.88 (0.22)	0.98 (0.26)	<0.001
Serum apolipoprotein A1 (g/L)	1.22 (9.19)	1.19 (0.15)	0.21

Values are means (SD), medians (interquartile ranges) or percentages. Higher adult socioeconomic status score means lower socioeconomic status. LTPA, leisure-time physical activity; IMT, intima-media thickness; NCEP, National Cholesterol Education Program.[29,44]; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

A 1-SD change in the triglyceride factor derived using a promax rotation was also associated with a 1.5–1.6-fold increase in the risk of hypertension (*Table 5*). The second-order dyslipidaemia factor was even more strongly associated.

Discussion

In this study, new-onset hypertension was preceded by dyslipidaemia characteristic of the metabolic syndrome in middle-aged men. Abnormal triglyceride and LDL metabolism seemed to be most strongly associated with the development of hypertension.

Of note, overall or abdominal obesity and hyperinsulinaemia did not explain the association of dyslipidaemia with incident hypertension, even though obesity, especially central obesity, and hyperinsulinaemia are independent predictors of hypertension.[12,13,33] Thus, these findings extend those from Physicians' Health Study[11] and other prospective cohort studies,[12–14] suggesting that underlying insulin resistance and other features associated with the metabolic syndrome do not explain the association of dyslipidaemia with the new-onset hypertension. Inflammation is related to abdominal obesity, the metabolic syndrome,[23,34] cardiovascular disease[35,36] and the development of hypertension,[33,37] but adjustment for C-reactive protein concentrations and carotid intima-media thickness did not alter the association of dyslipidaemia with incident hypertension.

In multiple regression analysis of the lipid, lipoprotein and apolipoprotein variables separately, 1-SD increments in the concentrations of triglycerides and apolipoprotein B and triglyceride content of HDL cholesterol were associated with a 1.4–1.8-fold higher risk of developing hypertension. Interestingly, adjustment for baseline systolic blood pressure had no effect on the relations. The associations were also similar in analyses stratified by median systolic blood pressure at baseline, indicating that higher blood pressure at baseline does not mediate the association. In multiple logistic regression analyses including all the lipid variables simultaneously, variables reflecting disturbed metabolism of LDL (especially HDL-triglyceride content and apolipoprotein B, but also LDL cholesterol) were associated

Table 2 Correlation coefficients of lipoprotein, apolipoprotein, and lipid variables with the factors derived from extraction and varimax and promax rotations. Correlations with waist, insulin concentrations, and baseline systolic and diastolic blood pressure are also shown

	Waist	Insulin	SBP	DBP	LDL	HDL	TG	LDL TG	HDL TG	Apo B	Apo A1
LDL	0.03	0.01	0.04	−0.01							
HDL	−0.29	−0.40	0.00	0.04	0.01						
TG	0.38	0.54	0.11	0.09	0.24	−0.45					
LDL TG	0.19	0.29	0.10	0.10	0.41	−0.30	0.66				
HDL TG	0.17	0.30	0.19	0.02	0.02	−0.15	0.64	0.54			
Apo B	0.29	0.38	0.03	0.06	0.66	−0.33	0.78	0.65	0.39		
Apo A1	−0.14	−0.19	0.02	0.09	0.08	0.82	−0.07	−0.07	0.10	0.00	
Varimax											
TG factor	0.26	0.45	0.16	0.03	0.02	−0.27	**0.85**	**0.71**	**0.91**	**0.57**	0.09
HDL factor	−0.19	−0.27	0.00	0.03	0.07	**0.94**	−0.21	−0.13	0.08	−0.12	**0.96**
LDL factor	0.08	0.13	0.00	−0.01	**0.96**	−0.07	**0.30**	**0.44**	−0.11	**0.75**	0.05
Promax											
TG factor	0.29	0.49	0.15	0.02	0.22	**0.37**	**0.80**	**0.85**	**0.73**	**0.73**	0.00
HDL factor	−0.23	−0.34	0.00	0.01	0.00	**0.96**	**−0.34**	0.25	−0.03	−0.25	**0.94**
LDL factor	0.15	0.25	0.00	−0.01	**0.93**	−0.18	**0.50**	**0.61**	0.11	**0.87**	0.01
Second order factor (Promax rotation)											
Dyslipidaemia factor	0.31	0.49	0.09	−0.01	**0.57**	**−0.62**	**0.84**	**0.80**	**0.51**	**0.89**	**−0.32**

For factor analysis, only the lipid, lipoprotein, and apolipoprotein variables were included for extraction and rotation. For the absolute value of $r \geq 0.20$, $P < 0.001$; for the absolute value of $r \geq 0.15$, $P < 0.01$; for the absolute value of $r > 0.10$, $P < 0.050$. For the factors derived from factor analysis, factors with loadings ≥ 0.60 were considered to be heavily loaded by a particular lipid, lipoprotein or apolipoprotein variable, 0.40–0.59 to be moderately loaded, and 0.30–0.39 to be modestly loaded. Modest to heavy loadings are in bold. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; Apo, apolipoprotein.

Table 3 Odds ratios (95% confidence interval) of developing hypertension during the 7-year follow-up for a 1-SD change in lipoprotein, apolipoprotein, and lipid fractions in 311 middle-aged men without hypertension at baseline

Variable (for a 1-SD change)	Model 1	Model 2	Model 3	Model 4
LDL cholesterol	1.30 (1.01–1.67)	1.30 (1.01–1.69)	1.34 (1.03–1.74)	1.27 (0.97–1.67)
HDL cholesterol	0.67 (0.50–0.89)	0.67 (0.50–0.88)	0.64 (0.47–0.86)	0.77 (0.55–1.08)
Apolipoprotein B	1.60 (1.24–2.08)	1.57 (1.21–2.05)	1.61 (1.23–2.12)	1.43 (1.06–1.92)
Apolipoprotein A1	0.88 (0.68–1.14)	0.87 (0.67–1.08)	0.86 (0.65–1.13)	1.01 (0.75–1.36)
Triglycerides	1.76 (1.35–2.29)	1.72 (1.31–2.26)	1.79 (1.34–2.39)	1.63 (1.17–2.27)
LDL triglyceride	1.46 (1.13–1.89)	1.44 (1.10–1.85)	1.42 (1.09–1.86)	1.25 (0.94–1.68)
HDL triglyceride	1.63 (1.25–2.12)	1.54 (1.18–2.01)	1.60 (1.22–2.12)	1.52 (1.13–2.05)

Lipoprotein, apolipoprotein, and lipid fractions were entered separately into the multivariable models. LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.
Model 1: adjusted for age.
Model 2: adjusted for age and systolic blood pressure at baseline.
Model 3: adjusted for age, smoking (never-smoker, former smoker, and current smoker), alcohol intake (g/week), adult socioeconomic status, leisure-time physical activity, presence of cardiovascular disease, and presence of diabetes.
Model 4: adjusted for the variables in model 3 and waist girth, concentrations of insulin, glucose and C-reactive protein, maximal carotid intima media thickness and baseline systolic blood pressure.

with a 2.3–2.6-fold increased risk of hypertension even after extensive adjustment of potential confounders or mediating factors. However, these measures are biologically and statistically intercorrelated, and these results should be viewed with caution. We therefore applied factor analysis as a complementary analysis.

Factor analysis is a technique wherein a large set of intercorrelated variables are reduced to one or more underlying

factors. Factor analysis has not previously been applied to interrelated lipid, lipoprotein, and apolipoprotein measures in the prediction of hypertension. The 'triglyceride' factor explained most of the variance of lipid, lipoprotein, and apolipoprotein concentrations both when using a varimax rotation and when using a promax rotation. With the varimax rotation, the 'triglyceride' factor seemed to primarily explain new-onset hypertension, whereas the 'LDL' factor only tended to be associated with new-onset hypertension. The varimax rotation produces uncorrelated factors, however, which facilitates interpretation, but which may not be relevant biologically.[28]

The promax rotation allows derivation of correlated factors, which can then be rotated in a second-order factor analysis.[28] The promax analyses yielded similar first-order factors as the varimax rotation, but as expected, the factors were intercorrelated. The first-order triglyceride factor from the promax rotation also predicted incident hypertension. In the second-order factor analysis of these factors, a single 'dyslipidaemia' factor was derived, which was a strong determinant of new-onset hypertension. Based on the perhaps biologically more relevant promax rotation and second-order factor analysis,[28] the many interwoven pathological processes characteristic of dyslipidaemia in the metabolic syndrome likely predispose to hypertension, rather than a single specific feature or subset of traits of dyslipidaemia.

How may dyslipidaemia provoke hypertension? The mechanisms remain speculative, but the endothelium likely plays an important role. Endothelial dysfunction is integral not only in the pathogenesis of atherosclerosis, thrombosis and insulin resistance, but also in hypertension. Triglyceride-rich lipoproteins and LDL cholesterol have been shown to be toxic to endothelial cells, whereas HDL cholesterol may be protective.[16] Therefore, long-term damage to the endothelium may lead to increased peripheral vascular resistance and thus to arterial hypertension. Dyslipidaemia may also cause hypertension by increasing arterial stiffness. Dyslipidaemia and other features related to insulin resistance were associated with decreased arterial compliance of the carotid artery in the Bogalusa Heart Study.[38]

There may exist other mediators, like the recently identified member of the nuclear hormone receptor family, liver X receptor (LXR, also known as NR1H3), which is a potential regulator of renin expression. Daugherty *et al.*[39] have shown in mice that hypercholesterolemia is associated with increased levels of circulating angiotensinogen and angiotensin peptides and that all the components of the renin–angiotensin–aldosterone system (RAAS), including renin, are overexpressed within atherosclerotic lesions. Of note, LXRα is physiologically activated during lipid loading, and the expression and activation of LXRα inside the atherosclerotic plaque have also been described.[40] Thus LXRα and other nuclear hormone receptors may in fact represent

Table 4 Odds ratios (95% confidence interval) of developing hypertension during the 11-year follow-up according to 1-SD changes in lipoprotein concentrations and high-density lipoprotein triglyceride content in 311 middle-aged men without hypertension at baseline

Variable	Odds ratio (95% confidence interval)
LDL cholesterol (1.0 mmol/L change)	1.29 (1.00–1.68)
HDL cholesterol (0.28 mmol/L change)	0.68 (0.51–0.92)
HDL triglyceride content (0.04 mmol/L change)	1.47 (1.13–1.92)

Stepwise backward logistic regression with age, concentrations of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides; LDL triglyceride content, HDL triglyceride content; and concentrations of apolipoprotein B and apolipoprotein A1 as continuous variables.

Table 5 Odds ratios (95% confidence interval) of developing hypertension during the 7-year follow-up according to 1-SD changes of factors derived from the varimax and promax rotations in 311 middle-aged men without hypertension at baseline

	Model 1	Model 2	Model 3	Model 4
Varimax rotation				
TG factor	1.53 (1.13–2.09)	1.58 (1.21–2.05)	1.64 (1.24–2.17)	1.55 (1.13–2.11)
HDL factor	0.80 (0.61–1.06)	0.79 (0.60–1.04)	0.77 (0.58–1.04)	0.88 (0.64–1.22)
LDL factor	1.27 (0.98–1.65)	1.28 (0.98–1.68)	1.29 (0.99–1.69)	1.22 (0.92–1.61)
Promax rotation, first-degree factors				
TG factor	1.59 (1.19–2.13)	1.51 (1.11–2.03)	1.56 (1.14–2.14)	1.51 (1.07–2.13)
HDL factor	0.85 (0.64–1.12)	0.83 (0.62–1.10)	0.82 (0.60–1.11)	0.93 (0.67–1.29)
LDL factor	1.15 (0.85–1.56)	1.15 (0.85–1.56)	1.16 (0.86–1.57)	1.11 (0.82–1.51)
Promax rotation, second-degree factor				
Dyslipidaemia factor	1.78 (1.36–2.33)	1.75 (1.33–2.30)	1.80 (1.36–2.40)	1.58 (1.14–2.18)

Adjusted for the variables in *Table 3* and for the varimax and first-degree promax factors, the other factors are derived from the analysis.

major mediators of cross-talk among lipid metabolism disorders, the RAAS, and blood pressure regulation.

If lipid disturbances provoke hypertension, it is logical that pharmacological treatment of dyslipidaemia lowers blood pressure. The large Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[41] and the Brisighella Heart Study[42] have found a small decrease in blood pressure with fibrates[41,42] and statins.[42] In a recent meta-analysis of randomized controlled trials of statin therapy, statin use decreased systolic blood pressure by 1.9 mmHg compared with placebo. In those with high normal or high blood pressure, the mean decrease was 4.0 mmHg.[43]

A limitation of this population-based study is the relatively small number of subjects. However, blood pressure at baseline and follow-up was measured accurately with a standardized protocol, rather than relying on self-reported hypertension. Moreover, extensive adjustment for potential confounding or mediating factors related to lifestyle and insulin resistance was done. In addition to clinically used lipid and lipoprotein measures, we also assayed apolipoproteins and the triglyceride content of lipoprotein fractions to provide a much broader picture of the dyslipidaemia characteristic of the metabolic syndrome. Similar results using logistic regression and factor analysis as complementary analytical approaches reinforce the findings and provide additional insight. It is nonetheless possible that residual confounding remains, and that underlying metabolic, genetic or environmental influences explain the association of dyslipidaemia with the development of hypertension. Also, extrapolation to other ethnic groups and women must be viewed with caution.

Dyslipidaemia characteristic of the metabolic syndrome predicted the development of hypertension during a 7-year follow-up of middle-aged men. The recognition of dyslipidaemia characteristic of the metabolic syndrome and initiation of lifestyle treatment even in the absence of hypertension is likely to reduce the long-term burden of cardiovascular disease. Furthermore, these epidemiological associations may fuel studies on the biological mechanisms linking lipid metabolism to blood pressure regulation.

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References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;**37**:1595–1607.
2. Kannel WB. Cardioprotection and antihypertensive therapy: The key importance of addressing the associated coronary risk factors (the Framingham experience). *Am J Cardiol* 1996;**77**: B6–B11.
3. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;**81**:7B–12B.
4. Ginsberg HN. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation* 2002;**106**: 2137–2142.
5. Carmena R, Duriez P, Fruchart J-C. Atherogenic lipoprotein particles in atherosclerosis. *Circulation* 2004;**109**:III-2–7.
6. Gotto J, Antonio M. Evolving concepts of dyslipidemia, atherosclerosis, and cardiovascular disease: The Louis F. Bishop lecture. *J Am Coll Cardiol* 2005;**46**:1219–1224.
7. Groop L, Orho-Melander M. The dysmetabolic syndrome. *J Intern Med* 2001;**250**:105–120.
8. Laaksonen DE, Niskanen L, Lakka H-M, Lakka TA, Uusitupa M. Epidemiology and treatment of the metabolic syndrome. *Ann Med* 2004;**36**:332–346.
9. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Ann Intern Med* 2003;**139**:761–776.
10. Kim J-A, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 2006;**113**: 1888–1904.
11. Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Michael Gaziano J. Dyslipidemia and the risk of incident hypertension in men. *Hypertension* 2006;**47**:45–50.
12. Hunt SC, Stephenson SH, Hopkins PN, Williams RR. Predictors of an increased risk of future hypertension in Utah. A screening analysis. *Hypertension* 1991;**17**:969–976.
13. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Metabolic precursors of hypertension. The San Antonio Heart Study. *Arch Intern Med* 1996;**156**:1994–2001.
14. Sesso HD, Buring JE, Chown MJ, Ridker PM, Gaziano JM. A prospective study of plasma lipid levels and hypertension in women. *Arch Intern Med* 2005;**165**:2420–2427.
15. Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet* 1997; **350**(Suppl. 1):SI20–SI23.
16. O'Connell BJ, Genest J Jr. High-density lipoproteins and endothelial function. *Circulation* 2001;**104**:1978–1983.
17. Vogel RA. Cholesterol lowering and endothelial function. *Am J Med* 1999;**107**:479–487.
18. Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res* 1988;**20**:46–50.
19. Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;**157**:2413–2446.
20. World Health Organization-International Society of Hypertension. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999;**17**:151–183.
21. Fruchart JC, Kora I, Cachera C, Clavey V, Duthilleul P, Moschetto Y. Simultaneous measurement of plasma apolipoproteins A-I and B by electroimmunoassay. *Clin Chem* 1982;**28**:59–62.
22. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998;**15**:539–553.
23. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen T-P, Valkonen V-P, Salonen R, Salonen JT. C-reactive

protein and development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia* 2004;**47**:1403–1410.
24. Lynch JW, Kaplan GA, Cohen RD, Kauhanen J, Wilson TW, Smith NL, Salonen JT. Childhood and adult socioeconomic status as predictors of mortality in Finland. *Lancet* 1994;**343**: 524–527.
25. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 2002;**25**:1612–1618.
26. Laaksonen DE, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT. Dietary and serum linoleic and polyunsaturated fatty acids predict cardiovascular mortality in middle-aged men. *Arch Intern Med* 2005; **165**:193–199.
27. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 1993;**87**: II56–II65.
28. Hu FB. Re: 'Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome'. *Am J Epidemiol* 2001;**153**:717–718.
29. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**:2709–2716.
30. Lakka TA, Laaksonen DE, Lakka H-M, Männikkö N, Niskanen LK, Rauramaa R, Salonen JT. Sedentary lifestyle, poor cardiorespiratory fitness and the metabolic syndrome. *Med Sci Sports Exerc* 2003;**35**:1279–1286.
31. Stevens J. *Applied Multivariate Statistics For The Social Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1986.
32. Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 2000;**152**:908–911; discussion 12.
33. Niskanen L, Laaksonen DE, Nyyssönen K, Punnonen K, Valkonen VP, Fuentes R, Tuomainen TP, Salonen R, Salonen JT. Inflammation, abdominal obesity, and smoking as predictors of hypertension. *Hypertension* 2004;**44**:859–865.
34. Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muche R, Brenner H, Koenig W. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 2000;**23**:1835–1839.
35. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;**98**: 731–733.
36. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen T-P, Salonen JT. C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study. *Eur Heart J* 2005;**26**:1783–1789.
37. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003;**290**:2945–2951.
38. Urbina EM, Srinivasan SR, Kieltyka RL, Tang R, Bond MG, Chen W, Berenson GS Correlates of carotid artery stiffness in young adults: The Bogalusa Heart Study. *Atherosclerosis* 2004;**176**:157–164.
39. Daugherty A, Rateri DL, Lu H, Inagami T, Cassis LA. Hypercholesterolemia stimulates angiotensin peptide synthesis and contributes to atherosclerosis through the AT1A receptor. *Circulation* 2004; **110**:3849–3857.
40. Zelcer N, Tontonoz P. Liver X receptors as integrators of metabolic and inflammatory signaling. *J Clin Invest* 2006;**116**:607–614.
41. The FIELD study i. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *The Lancet* **366**: 1849–1861.
42. Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. *Am Heart J* 2004; **148**:285–292.
43. Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure?: A meta-analysis of randomized, controlled trials 10.1161/01.HYP.0000259737.43916.42. *Hypertension* 2007;**49**:792–798.
44. National Cholesterol Education Program. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–2497.