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Determinants of lumbar artery occlusion among patients with sciatica: A three-year follow-up with magnetic resonance angiography

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Abstract We showed previously that chronic *Chlamydia pneumoniae* infection increases the risk of lumbar artery occlusion. We did not evaluate, however, the effect of other risk factors for cardiovascular diseases in combination with this chronic infection. The purpose of this study was to investigate the combined effect of chronic *C. pneumoniae* infection and other known determinants of artery occlusion in a population of sciatica patients. Two-dimensional time-of-flight magnetic resonance angiography (MRA) was used to evaluate lumbar arteries at baseline and three years. The arteries on both sides (L1–L4) were evaluated visually and scored as normal, narrowed or occluded. Logistic regression analysis was performed separately for baseline total arterial stenosis and each L1–L4 segmental artery pair, and for incident new stenosis during the follow-up period. The determinants analyzed included age, body mass index (BMI, kg/m²), education, gender, and smoking, in addition to presence of chronic *C. pneumoniae* infection. MRA was obtained at baseline for 147 patients and at 3 years for 134 patients. Sixty-four (47.8%) of 134 patients had new arterial stenosis. Total incidence of new arterial stenosis was

distributed quite evenly between the individual segmental levels, varying from 12.7 to 18.6%. BMI was the only predictor of new arterial stenosis (odds ratio (OR) 1.13). A reasonable logistic model could be established only for baseline L4 and total arterial scores. At L4, education was a protective factor (OR 0.07), whereas age (OR for the oldest age group 6.7) and BMI (OR 1.17) were associated with increased risk of occlusion. For total arterial score, chronic *C. pneumoniae* infection was an independent determinant of arterial occlusion, increasing the risk to almost eightfold. Additionally, BMI (OR 1.16), and age (for the oldest age group OR 11.4) were significant determinants for stenosis. Smoking was not statistically significant. As chronic *C. pneumoniae* infection was an independent determinant of lumbar artery occlusion, treatments of this chronic infection may have an impact on lumbar diseases. The importance of BMI for new arterial stenosis suggests that weight reduction may also have a beneficial effect in lumbar artery disease.

Keywords Arterial stenosis · Magnetic resonance imaging · *Chlamydia pneumoniae* · Risk factors · Sciatica

Introduction

Atherosclerosis starts early. This first came to light in the 1950s, when many soldiers under 20 years of age who died in the Korean war were found to have atheromatous lesions in coronary arteries [31]. The atherosclerotic process in the lumbar arteries, however, is not yet fully understood. In the lumbar region four artery pairs supply the first through the fourth lumbar segment, while the fifth segment is nourished by branches of the middle sacral artery originating in the aortic bifurcation. A theory of low back pain (LBP) due to lumbar artery disease was proposed in mid-1990s [13]. On the basis of cadaver studies, intervertebral disc degeneration was associated with advanced aortic atherosclerotic lesions [16], and stenotic changes in lumbar arteries associated with chronic LBP [14, 17].

In the population-based Framingham cohort, advanced aortic atherosclerosis presenting as calcified deposits in the posterior wall of the aorta preceded intervertebral disc deterioration and was also associated with LBP [15], and predicted subsequent vascular morbidity and mortality [35]. An association between aortic atherosclerosis and LBP was also found by Kurunlahti et al. [19]. However, both a large population-based survey and a nested case-control study of Finnish farmers found no association between LBP and ischemic heart disease [8, 27].

Atherosclerotic cardiovascular diseases and LBP share common risk factors. These include smoking [3, 5, 28], obesity [11, 22], and socioeconomic status [18, 25, 32].

Chlamydia pneumoniae is a common respiratory pathogen, which tends to give rise to chronic infections [34]. Its association with coronary heart disease has been reported convincingly [2, 30]. Recently, we found that chronic *C. pneumoniae* infection was strongly associated with the occlusion of lumbar arteries among sciatica patients—especially at the L4-segment level [12]. However, in the previous study, we did not evaluate the effect of other cardiovascular risk factors. It might well be that chronic *C. pneumoniae* has no independent effect on lumbar artery disease, but rather acts as a risk indicator for other underlying causal factors. Therefore, the aim of this study was to investigate the combined effect of chronic *C. pneumoniae* infection and other risk factors on artery occlusion in a population of sciatica patients using a non-invasive imaging technique, magnetic resonance angiography (MRA) of lumbar arteries.

Methods

Subjects

The baseline study population consisted of 147 (88 men, mean age 43.4 years; 59 women, mean age 45.0 years)

non-operated sciatica patients with unilateral symptoms for 1–6 months. Three years later these patients were invited to a follow-up MRA assessment; nine refused, two were not reached, one had a pace-maker, and one had died. Thus, 134 patients were re-scanned at 3 years. The study was approved by the local ethics committee.

Imaging

The patients were scanned with a 1.5-T scanner (GE Signa Echospeed; GE Medical Systems, Milwaukee, WI) at baseline and at three years. A phased-array spine cervico-thoracic-lumbar coil was utilized for MRA of the lumbar arteries. Two-dimensional (2D) time-of-flight (TOF) MRA was used to evaluate the patency of the lumbar arteries. Magnetic resonance (MR) images were obtained in the coronal direction to cover the area of the lumbar spine using a 5.1 ms time of echo, 29 ms time of repetition, 60° flip angle, 256×512 matrix and 30×30 cm field-of-view, and 1.5 mm slice thickness. A spatial presaturation pulse was placed posterior to the imaging slices in order to suppress the signal from the lumbar veins. The MRA scans of the corresponding artery pairs were analyzed by an experienced radiologist who was blinded to all other findings. A workstation (Advantage windows; GE Medical Systems) was used in the image analysis.

Image Analysis

The lumbar arteries on both sides from L1 to L4 were evaluated visually and scored as normal (0), narrowed (1) or occluded (2). A score for lumbar disease was calculated by summing up the scores of the eight individual arteries (total arterial score). An artery was classified as narrowed if the diameter of the vessel was stenosed by at least one-third, and as occluded if it was not detectable. In the evaluation, the contralateral artery and the next artery above were used as reference. The fifth lumbar segment was not analyzed because it receives its blood supply from the middle sacral artery and through the branches of the iliolumbar arteries, and the direction of these arteries could not be visualized in the 2D-TOF scan at the same time as the other lumbar arteries. Both maximum intensity projections (anteroposterior, oblique, and lateral views) and coronal source images were used to determine stenosis of the lumbar arteries. The incidence of newly formed stenosis was defined as the difference between the arterial scores at baseline and at three years.

Determinants

The determinants analyzed included age (years) and body mass index (BMI, kg/m²) at baseline, education

(college or higher vs no college), smoking at least ten cigarettes per day at baseline or three years), and presence of chronic *C. pneumoniae* infection. Additionally, gender was included in the statistical models. Patient-reported data was used for BMI, education and smoking. Presence of chronic *C. pneumoniae* infection was evaluated with specific antibodies from two blood samples taken at least one month apart from each other. The analytic method and criteria for the presence of chronic infection have been described earlier [12].

Statistical analysis

Logistic regression analysis was performed separately for baseline total arterial stenosis, each L1–L4 segmental artery pair at baseline, and for incident new stenosis during the three-year follow-up period. Odds ratios (OR) and 95% confidence intervals (95% CI) were considered. For baseline arterial stenosis score, a classification of no changes or one artery narrowed (score ≤ 1) vs more pervasive stenotic changes (score ≥ 2) was used. For each segmental artery pair and for new incident stenosis, a classification of no stenosis vs any stenosis was used. At first all the potential determinants were forced into the model, but finally a model with the highest explanatory power for arterial occlusion was generated. Statistical analyses were performed with SPSS 11.0 software (SPSS Corporation, Chicago, IL), and *P*-values of less than 0.05 were considered significant.

Results

Status of lumbar arteries in MRA

At baseline, a total of 1176 lumbar arteries from 147 patients were examined, of which 957 (81%) were classified as normal and 219 (19%) as narrowed or occluded. L4 segmental arteries were most frequently occluded (Fig. 1). At 3 years, a total of 1,072 lumbar arteries from 134 patients were examined, of which 785 (73%) arteries were classified as normal and 287 (27%) as narrowed or occluded. Over the follow-up period of 3 years, new arterial stenosis was observed in 64 (47.8%) of 134 patients. Forty (29.9%) patients had an increase of one grade, 18 (13.4%) two grades, and six (4.5%) three grades or more in arterial score. Total incidence of new arterial stenosis was distributed quite evenly between the individual segmental levels, varying from 12.7% to 18.6% (Fig. 2).

Determinants

Descriptive data on selected determinants of lumbar artery occlusion both at baseline and at three years are

Fig. 1 Boxplot of baseline L1–L4 segmental and total arterial stenosis score. Hatched lines represent medians, lower border of the box (if present) lower quartile (Q1) and upper border of the box (if present) the upper quartile (Q3), whiskers maximum values, “o” outliers (if values exceed $1.5 \times (Q3 - Q1)$), and crosses (*) extreme values (if values exceed $2 \times (Q3 - Q1)$)

presented in Table 1. BMI at three years was not evaluated. The proportions of patients with college education, who were permanent smokers, and who had chronic *C. pneumoniae* infection did not change markedly during the follow-up period.

Fig. 2 Incidence of new stenosis over the three-year follow-up. Percentage of patients (of total 134 patients) with new incident stenosis is presented separately for total lumbar score (combined segments L1–L4) and for the individual levels. Arteries, which remained unchanged during the follow-up are not presented. Difference in the arterial score means a corresponding increase in stenosis score (e.g., a difference of 1 means that one normal artery was narrowed or one narrowed artery was occluded)

Table 1 Determinants of lumbar artery occlusion at baseline and three years. For ordinal variables number of patients (percentage) and for continuous variables mean value ($\pm$ standard deviation) are presented

Determinant	Baseline (<i>N</i> = 147)		Three years (<i>N</i> = 134)	
	<i>N</i>	%	<i>N</i>	%
Female	59	40.1	52	38.8
Smoker	28	19.0	26	19.4
<i>C. pneumoniae</i> infection	14	9.5	13	9.7
College education	24	16.3	22	16.4
Age (years)	44 $\pm$ 13		46 $\pm$ 13	
Body mass index (kg/m ²)	25.5 $\pm$ 3.6		n.a.	

n.a. = not assessed

Preliminary logistic regression model

In the preliminary logistic regression model, baseline total arterial stenosis score associated significantly with age (OR for the oldest age group 10.6; 95% CI 3.7–30.0), BMI (OR 1.15; 95% CI 1.04–1.31) and *C. pneumoniae* infection (OR 8.6; 95% CI 1.5–47.7) (Table 2). The model correctly predicted 83.3% of patients with an arterial score of 1 or less, and 71.4% of more stenotic patients. Baseline L1–L3 segmental stenosis associated weakly with age, and the models poorly predicted stenosis at these levels (Table 2). L4 segmental artery stenosis associated with age (for the oldest age group OR

4.7; 95% CI 1.8–12.2) and BMI (OR 1.18; 95% CI 1.05–1.33). At this level, the model correctly predicted 75.3% of patients with no arterial stenosis, and 66.2% of stenotic patients (Table 2). Baseline BMI—but not age or any other determinant—was the only predictor of new stenosis during the three-year follow-up period (OR 1.13; 95% CI 1.01–1.28) (Table 2).

Final logistic regression model

No reasonable model could be established for segmental stenosis at L1–L3 or for new incident stenosis. The final model for baseline L4 stenosis included chronic *C. pneumoniae* infection, education, age, and BMI (Table 3). Education (college or higher) was a protective factor (OR 0.07; 95% CI 0.01–0.91), whereas BMI (OR 1.17; 95% CI 1.04–1.31) and age (for the oldest group OR 6.7; 95% CI 2.2–20.9) were significant risk factors for stenosis of score 2 or more. Chronic *C. pneumoniae* infection was of borderline significance (OR 3.9; 95% CI 1.0–15.5). The model predicted correctly 98.2% of patients with arterial scores of 1 or less, and 48.6% of more stenotic cases (Table 3).

The final model for baseline total arterial stenosis included smoking, chronic *C. pneumoniae* infection, age, and BMI (Table 3). Chronic *C. pneumoniae* infection (OR 7.7; 95% CI 1.4–41.8), BMI (OR 1.16; 95% CI 1.04–1.31), and age (for the oldest age group OR 11.4;

Table 2 Logistic regression models with baseline lumbar artery occlusion (segmental artery pair at L1–L4 and total arterial score) and incident new stenosis over the three-year follow-up as depen-

dent variables. All the potential determinants are included, except *C. pneumoniae* infection at L4. Odds ratios (OR) and 95% confidence intervals (CI) for ORs in each model are presented

	Arterial stenosis ^a										New incident stenosis ^a							
	L1			L2		L3		L4		Total								
	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI			
BMI (kg/m ²)	1.09		0.97–1.22	1.14*		1.01–1.30	1.11		1.00–1.24	1.18**		1.05–1.33	1.15*		1.04–1.31	1.13*		1.01–1.28
Age (years)																		
41–50 years ^b	2.1		0.7–6.2	14.5**		2.7–78.2	0.9		0.3–2.5	1.2		0.5–2.9	1.9		0.8–4.9	1.4		0.6–3.1
50 years or more ^b	5.3**		1.8–16.0	7.6*		1.3–44.3	4.1**		1.5–10.7	4.7**		1.8–12.2	10.6**		3.7–30.0	0.6		0.2–1.6
<i>C. pneumoniae</i> infection																		
Chronic ^b	2.0		0.5–7.4	3.2		0.7–13.8	2.3		0.6–9.0	n.a.		–	8.6*		1.5–47.7	3.0		0.8–11.4
Education																		
College ^b	1.4		0.4–4.9	1.9		0.5–8.1	0.4		0.1–1.6	0.6		0.2–1.7	0.6		0.2–2.2	0.6		0.2–1.6
Smoking																		
Now or previously ^b	2.5		0.9–6.9	2.7		0.8–8.8	1.0		0.4–2.7	1.7		0.7–4.3	1.7		0.6–4.4	0.5		0.2–1.3
Gender																		
Female ^b	2.1		0.9–5.0	1.8		0.6–5.0	1.2		0.5–2.8	1.5		0.7–3.3	1.4		0.6–3.1	0.9		0.4–2.0
Correctly predicted (%) with total <i>n</i> (<i>N</i>)																		
No stenosis	95.5 (112)			97.6 (123)			93.4 (106)			75.3 (73)			83.3 (84)			70.0 (70)		
Stenosis ^a	17.1 (35)			20.8 (24)			39.0 (41)			66.2 (74)			71.4 (63)			56.3 (64)		

^aModels predicted arterial stenosis score ≥ 1 at the levels L1–L4, total arterial stenosis score ≥ 2 and new incident stenosis ≥ 1

^bCompared to comparison group of subjects with no risk or protective factor present

BMI, body mass index; n.a., not assessed

Significance ranked: ** $P < 0.01$, * $0.01 \leq P < 0.05$

Table 3 Determinants in the final models predicting baseline L4-segment and total arterial score ≥ 2 . Odds ratios (OR) and 95% confidence intervals (CI) for ORs are presented

	L4		Total	
	OR	P 95% CI	OR	P 95% CI
BMI (kg/m ²)	1.17*	1.04–1.31	1.16*	1.04–1.31
Age (years)				
40 years or less ^a	1.0		1.0	
41–50 years	1.7	0.5–5.5	2.0	0.8–5.1
50 years or more	6.7*	2.2–20.9	11.4*	4.0–31.9
<i>C. pneumoniae</i> infection				
Not chronic ^a	1.0		1.0	
Chronic	3.9	1.0–15.5	7.7*	1.4–41.8
Education				
Less than college ^a	1.00			
College	0.07*	0.01–0.91	n.a.	
Smoking				
Not ^a				
Now or previously	n.a.		1.7	0.7–4.4
Correctly predicted (%) with total <i>n</i> (<i>N</i>)				
No stenosis		98.2 (112)		83.3 (84)
Stenosis ^a		48.6 (35)		71.4 (63)

^aComparison group

BMI, body mass index; n.a. = not assessed

Significance ranked: ** $P < 0.01$, * $0.01 \leq P < 0.05$

95% CI 4.0–31.9) emerged as significant determinants of total arterial stenosis. On the other hand, smoking was not statistically significant (OR 1.7; 95% CI 0.7–4.4). The model correctly predicted 83.3% of patients with arterial scores of 1 or less, and 71.4% of more stenotic ones (Table 3).

Discussion

This study revealed that chronic *C. pneumoniae* infection is an independent determinant of baseline total arterial stenosis, increasing the risk of occlusion to almost eightfold. In addition to *C. pneumoniae* infection, age, and BMI significantly associated with increased risk of occlusion (total score). However, BMI was the only predictor of new lumbar artery stenosis formation over the relatively brief follow-up period (Table 2).

The significant independent effect of chronic *C. pneumoniae* infection on total lumbar arterial stenosis is not surprising per se, as this pathogen has been detected in abdominal aortic aneurysms and atherosclerotic plaques in the vessel walls of the lower extremities [7, 10]. Furthermore, *C. pneumoniae* antibodies correlated strongly with intimal calcification of the femoral arteries in non-diabetic Finnish individuals [23]. A recent German study discovered a significant impact of infectious pathogen burden on the development of coronary artery disease [6]. However, the positive relation to the presence of coronary disease was shown only for some

pathogens, not all. These “atherosclerotic” pathogens were *C. pneumoniae*, cytomegalovirus, *Helicobacter pylori*, and herpes virus simplex type I. The association of pathogen burden with coronary artery disease was modulated by serum interleukin (IL)-6 levels.

The non-significant effect of smoking on arterial occlusion in the final model was unexpected, as cigarette smoking is a major cause of coronary heart disease and peripheral vascular disease. This manifests as an increased risk of thrombosis of narrowed vessels and as an increased degree of atherosclerosis in those vessels. Additionally, a dose–response relationship between atherosclerosis and both amount and duration of smoking has been found [5, 9]. In this study a significant proportion of patients were permanent smokers, as over 19% of them smoked at least half a pack per day both at baseline and three years. The expected significant contribution of smoking to arterial stenosis did not occur, however. This apparent conflict could be explained by *smoker's paradox*, a phenomenon of reduced risk for restenosis in smokers [1]. This is suggested to be caused by the effect of smoke-derived nitric oxide (NO) expression on a suppressed basal NO-production [33].

Age had a major effect on arterial stenosis at all segmental levels at baseline, which is not surprising as age is the main clinical determinant of large artery stiffness. Cross-sectional studies have shown that aortic and carotid stiffness increase with age by approximately 10–15% over a period of ten years. Among other cardiovascular risk factors, diabetes accelerates arterial stiffness, whereas the role of dyslipidemia and smoking is unclear. Furthermore, decreased carotid distensibility, increased arterial thickness, and presence of calcifications and plaques often coexist in the same subjects [4]. In this study, over the relatively short follow-up period of three years, age was not a significant risk factor for new arterial stenosis.

In a Finnish study of young adults, risk habits (imprudent diet, smoking, physical inactivity, and frequent inebriation with alcohol) showed significant clustering. Independent risk factors for risk habit clustering included male sex, aggressiveness, and past unemployment, whereas attention to health habits, higher education (being a student), good self-perceived health, and a high sense of responsibility seemed to be protective factors [29]. In the same cohort it was shown that the least educated young adults adopted a more adverse lifestyle than the more educated [24]. Similarly, being overweight or obese has been observed to promote clusters of coronary heart disease in the Framingham Study cohort [11]. Furthermore, an accumulation of risk habits was associated with an atherogenic lipid and blood pressure profile (clustering of high density lipoprotein cholesterol/total cholesterol ratio, triglycerides, and diastolic blood pressure in their extreme tertiles) among young adults [29]. Such clustering might explain

why obesity is so weakly associated with LBP [22]. Importantly, an atherogenic lipid profile was also associated with both *C. pneumoniae* and *H. pylori* antibodies in healthy Finnish men [21], and chronic infections could be related to obesity and the metabolic syndrome via their effect on lipid and glucose metabolism [26]. Unfortunately we do not know the association of lipid profile with lumbar vascular disease as we did not measure lipids.

In this study, higher education was a protective factor at the L4 segment, whereas obesity was the only significant determinant of new lumbar artery stenosis. These effects could be explained by clustering of determinants like education, smoking, obesity, and chronic *C. pneumoniae* infection. Unfortunately—probably due to limited number of observations in some cells—no reasonable logistic models for the interaction terms could be obtained. However, in the chi-square test higher education tended to associate with lesser obesity and lesser proportion of smokers but not with lesser proportion of chronic *C. pneumoniae* infection (data not shown). This indicates that a clustering of education, smoking, and obesity may exist in this study population. It is not surprising that those individuals with a greater degree of knowledge about health-related factors behave in a “healthier” way. These results are comforting as they suggest that we can influence the status of lumbar arteries by our health-behavior (most likely by weight reduction).

We have recently observed that lumbar vascular stenosis predicts poor subjective physical ability during a three-year follow-up [20]. Additionally, newly formed lumbar arterial stenosis was associated with patient-reported medical consultations during the year preceding the baseline assessment and with prolonged LBP during the first year of follow-up but not with patient-reported recurrences of symptoms at later follow-up assessments. Because of this association between lumbar artery disease and subjective physical performance, it is clinically relevant to sort out the determinants of lumbar artery

occlusion. According to our hypothesis, lumbar artery occlusion causes intervertebral disc degeneration via diminished nutrition through the endplates ultimately leading to a lowered tissue tolerance, whereas MRA-assessed lumbar artery disease unlikely generates any stenotic claudication symptoms.

In the current study, we were able to establish the independent effect of chronic *C. pneumoniae* infection. The presence of this pathogen increased the risk of arterial occlusion substantially, irrespective of other known risk factors for cardiovascular diseases. The major drawback of the current study is the fact that the patients were in their forties. Ideally, lumbar vascular disease should be evaluated in a prospective long-term cohort study of young adults. Furthermore, the evaluation of *C. pneumoniae* infection should be included in such cohort studies. Future trials will elucidate whether treatment of this chronic infection has an impact on lumbar diseases.

Conclusions

At baseline, a total of 1,176 lumbar arteries from 147 sciatica patients were examined, of which 957 (81%) were classified as normal and 219 (19%) as narrowed or occluded. L4 segmental arteries were most frequently occluded. Over the follow-up period of three years, new arterial stenosis was observed in 64 (47.8%) of 134 patients. Total incidence of new arterial stenosis was distributed quite evenly between the individual segmental levels, varying from 12.7 to 18.6%. Baseline BMI was the only predictor of new stenosis during the three-year follow-up period (OR 1.13; 95% CI 1.01–1.28). For L4 segmental occlusion, education was a protective factor, whereas BMI and age increased the risk of stenosis. For the total baseline arterial score, chronic *C. pneumoniae* infection was an independent determinant of arterial occlusion, increasing the risk to almost eightfold. BMI and age were also significant determinants of stenosis.

References

1. Angeja BG, Kermgard S, Chen MS, McKay M, Murphy SA, Antman EM, Cannon CP, Braunwald E, Gibson CM (2002) The smoker's paradox: insights from the angiographic substudies of the TIMI trials. *J Thromb Thrombolysis* 13:133–139
2. Bachmaier K, Neu N, de la Maza LM, Pal S, Hessel A, Penninger JM (1999) Chlamydia infections and heart disease linked through antigenic mimicry. *Science* 283:1335–1339
3. Battie MC, Bigos SJ, Fisher LD, Hansson TH, Nachemson AL, Spengler DM, Wortley MD, Zeh J (1989) A prospective study of the role of cardiovascular risk factors and fitness in industrial back pain complaints. *Spine* 14:141–147
4. Benetos A, Waeber B, Izzo J, Mitchell G, Resnick L, Asmar R, Safar M (2002) Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *Am J Hypertens* 15:1101–1108
5. Burns DM (2003) Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis* 46:11–29
6. Georges JL, Rupprecht HJ, Blankenberg S, Poirier O, Bickel C, Hafner G, Nicaud V, Meyer J, Cambien F, Tiret L, AtheroGene Group (2003) Impact of pathogen burden in patients with coronary artery disease in relation to systemic inflammation and variation in genes encoding cytokines. *Am J Cardiol* 92:515–521

7. Gutierrez J, Linares-Palomino J, Lopez-Espada C, Rodriguez M, Ros E, Piedrola G, del Maroto MC (2001) Chlamydia pneumoniae DNA in the arterial wall of patients with peripheral vascular disease. *Infection* 29:196–200
8. Heliövaara M, Mäkelä M, Aromaa A, Impivaara O, Knekt P, Reunanen A (1995) Low back pain and subsequent cardiovascular mortality. *Spine* 20:2109–2111
9. Jee SH, Suh I, Kim IS, Appel LJ (1999) Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: the Korea Medical Insurance Corporation Study. *J Am Med Assoc* 282:2149–2155
10. Juvonen J, Juvonen T, Laurila A, Alakärppä H, Lounatmaa K, Surcel HM, Leinonen M, Kairaluoma MI, Saikku P (1997) Demonstration of *Chlamydia pneumoniae* in the walls of abdominal aortic aneurysms. *J Vasc Surg* 25:499–505
11. Kannel WB, Wilson PW, Nam BH, D'Agostino RB (2002) Risk stratification of obesity as a coronary risk factor. *Am J Cardiol* 90:697–701
12. Karppinen J, Mikkonen P, Kurunlahti M, Tervonen O, Paldanius M, Vasari P, Saikku P, Vanharanta H (2003) Chronic *Chlamydia pneumoniae* infection increases the risk of occlusion of lumbar segmental arteries of patients with sciatica: a 3-year follow-up study. *Spine* 28:E284–E289
13. Kauppila LI (1995) Can low-back pain be due to lumbar-artery disease? *Lancet* 346:888–889
14. Kauppila LI (1997) Prevalence of stenotic changes in arteries supplying the lumbar spine. A postmortem angiographic study on 140 subjects. *Ann Rheum Dis* 56:591–595
15. Kauppila LI, McAlindon T, Evans S, Wilson PW, Kiel D, Felson DT (1997) Disc degeneration/back pain and calcification of the abdominal aorta. A 25-year follow-up study in Framingham. *Spine* 22:1642–1647
16. Kauppila LI, Penttilä A, Karhunen PJ, Lalu K, Hannikainen P (1994) Lumbar disc degeneration and atherosclerosis of the abdominal aorta. *Spine* 19:923–929
17. Kauppila LI, Tallroth K (1993) Post-mortem angiographic findings for arteries supplying the lumbar spine: their relationship to low-back symptoms. *J Spinal Disord* 6:124–129
18. Kilander L, Berglund L, Boberg M, Vessby B, Lithell H (2001) Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. *Int J Epidemiol* 30:1119–1126
19. Kurunlahti M, Tervonen O, Vanharanta H, Ilkko E, Suramo I (1999) Association of atherosclerosis with low back pain and the degree of disc degeneration. *Spine* 24:2080–2084
20. Kurunlahti M, Karppinen J, Haapea M, Niinimäki J, Autio R, Vanharanta H, Suramo I, Tervonen O (2004) Three-year follow-up of lumbar artery occlusion with magnetic resonance angiography in sciatica patients. Associations between occlusion and patient-reported symptoms. *Spine* 29:1804–1808
21. Laurila A, Bloigu A, Näyhä S, Hassi J, Leinonen M, Saikku P (1997) Chronic *Chlamydia pneumoniae* infection is associated with a serum lipid profile known to be a risk factor for atherosclerosis. *Arterioscler Thromb Vasc Biol* 17:2910–2913
22. Leboeuf-Yde C (1999) Smoking and low back pain. A systematic literature review of 41 journal articles reporting 47 epidemiologic studies. *Spine* 24:1463–1470
23. Lehto S, Niskanen L, Suhonen M, Rönnemaa T, Saikku P, Laakso M (2002) Association between *Chlamydia pneumoniae* antibodies and intimal calcification in femoral arteries of nondiabetic patients. *Arch Intern Med* 162:594–599
24. Leino M, Raitakari OT, Porkka KV, Taimela S, Viikari JS (1999) Associations of education with cardiovascular risk factors in young adults: the Cardiovascular Risk in Young Finns Study. *Int J Epidemiol* 28:667–675
25. Leino-Arjas P, Kaila-Kangas L, Keskimäki I, Notkola V, Mutanen P (2002) Inpatient hospital care for lumbar intervertebral disc disorders in Finland in relation to education, occupational class, income, and employment. *Public Health* 116:272–278
26. Leinonen M, Saikku P (2002) Evidence for infectious agents in cardiovascular disease and atherosclerosis. *Lancet Infect Dis* 2:11–17
27. Penttinen J (1995) Risk of myocardial infarction among subjects visiting a doctor because of back disorder. A case-control study in Finnish farmers. *Spine* 20:2774–2776
28. Power C, Frank J, Hertzman C, Schierhout G, Li L (2001) Predictors of low back pain onset in a prospective British study. *Am J Public Health* 91:1671–1678
29. Raitakari OT, Leino M, Rakkonen K, Porkka KV, Taimela S, Räsänen L, Viikari JS (1995) Clustering of risk habits in young adults. The Cardiovascular Risk in Young Finns Study. *Am J Epidemiol* 142:36–44
30. Saikku P, Leinonen M, Mattila K, Ekman MR, Nieminen MS, Mäkelä PH, Huttunen JK, Valtonen V (1988) Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet* 2:983–986
31. Strong JP, McGill HCJ (1962) The natural history of coronary atherosclerosis. *Am J Pathol* 40:37–49
32. van Rossum CT, van de Mheen H, Witteman JC, Mackenbach JP, Grobbee DE (1999) Socioeconomic status and aortic atherosclerosis in Dutch elderly people: the Rotterdam Study. *Am J Epidemiol* 150:142–148
33. Wang XL, Raveendran M, Wang J (2003) Genetic influence on cigarette-induced cardiovascular disease. *Prog Cardiovasc Dis* 45:361–382
34. Ward ME (1995) The immunobiology and immunopathology of chlamydial infections. *APMIS* 103:769–796
35. Wilson PW, Kauppila LI, O'Donnell CJ, Kiel DP, Hannan M, Polak JM, Cupples LA (2001) Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation* 103:1529–1534