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Circulating soluble adhesion molecules ICAM 1 and VCAM 1 and incident coronary heart disease the PRIME Study

Luc, G., Arveiler, D., Evans, A., Amouyel, P., Ferrieres, J., Bard, J. M., Elkhail, L., Fruchart, J. C., Ducimetiere, P., & Study, P. R. I. M. E. (2003). Circulating soluble adhesion molecules ICAM 1 and VCAM 1 and incident coronary heart disease the PRIME Study. *Atherosclerosis*, 170(1), 169-176. [https://doi.org/10.1016/S0021-9150\(03\)00280-6](https://doi.org/10.1016/S0021-9150(03)00280-6)

Published in:
Atherosclerosis

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Associations between classical cardiovascular risk factors and coronary artery disease in two countries at contrasting risk for myocardial infarction: the PRIME Study

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Received 18 November 1999; received in revised form 23 March 2000; accepted 8 April 2000

Abstract

Purpose: In two countries with contrasting risk for coronary artery disease (CAD)—Northern Ireland and France—a case-control study was performed on baseline data within a cohort study to compare the strength of the associations between CAD prevalence and classical risk factors. **Method and results:** A sample of 9561 men, aged 50–60 years, was studied: 382 had had myocardial infarction or angina, and 9179 were controls. In both countries, variables associated with CAD were age, body mass index, hypertension, diabetes, family history of myocardial infarction (MI), tobacco consumption, triglycerides, HDL-cholesterol, apolipoprotein A-I and B levels. Logistic regression analyses were conducted using standardized odds ratios. The strength of the associations with CAD was rather similar in the two countries (Northern Ireland versus France) for age [1.26 (1.10–1.45) vs. 1.41 (1.17–1.69)], family history of MI [1.50 (1.04–2.15) vs. 1.83 (0.99–3.37)], hypertension [1.49 (1.13–1.97) vs. 1.67 (1.14–2.44)], diabetes [5.42 (2.53–11.60) vs. 2.24 (1.06–4.73)], tobacco consumption [1.43 (1.27–1.60) vs. 1.39 (1.22–1.58)], HDL-cholesterol [0.80 (0.68–0.94) vs. 0.86 (0.70–1.06)] and triglyceride levels [1.17 (1.01–1.36) vs. 1.10 (0.91–1.32)]. Discrepancies concerned lipoprotein(a) [1.22 (1.06–1.40) vs. 0.96 (0.81–1.15), $P < 0.01$], with stronger associations in Northern Ireland than in France. **Conclusion:** It is concluded that the higher prevalence of CAD in Northern Ireland cannot be explained by major differences in the susceptibility to classical risk factors; the difference in risk of CAD appears mainly related in Northern Ireland to other risk factors including a worse lipid profile and genetic/environmental interactions. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Apolipoproteins; Coronary artery disease; Epidemiological methods; Lipoproteins; Risk factors

1. Introduction

Since the 1970s, epidemiological studies have

demonstrated large international differences in coronary artery disease (CAD) incidence and mortality rates [1,2]. Several risk factors have been identified, and international surveys have been planned in order to investigate these cross-cultural differences in CAD morbidity and mortality [3,4]. Results, however, have shown that the measures of classical risk factors at a

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population level only explain part of this variability [5–7]. Further research was thus necessary, and it was aimed at the identification of new additional risk factors for CAD [8–10]. Lipoprotein(a), for example, was the focus of intensive research, and led to conflicting results in its association with CAD in populations [11–14]. Despite the emergence of such novel factors we have tried to assess the role of classical risk factors in explaining these intercountry differences in CAD risk [15–18].

The PRIME Study [19] (Prospective Epidemiological Study of Myocardial Infarction (MI)) is a prospective cohort study, designed to evaluate the contribution of nutritional, metabolic and genetic risk factors in the development of ischemic heart disease in Europe, with emphasis on those factors which might partially explain the incidence variability. The 5-year follow-up of the male cohorts enrolled in France and in Northern Ireland will be available in the year 2001. The description of the population under study has already been published, and it was shown that estimates of the individual's chance of developing a major CAD event calculated from available multiple logistic functions scores, combining age, cigarette smoking, blood pressure, total cholesterol and body mass index, were of the same order of magnitude in Belfast, Lille and Strasbourg, slightly higher than in Toulouse [19]. Using the baseline data from The PRIME Study, a case-control study was carried out to determine whether a higher prevalence of CAD in Northern Ireland than in France could be explained by a difference in the susceptibility to risk factors. Our aim was to compare the strength of associations between prevalence of CAD morbidity and the prevalence of classical risk factors (an extended list of CAD risk factors in comparison with the previous work [19]), with identical methodology and unique data set, in two European neighboring countries at contrasting risk for CAD.

2. Materials and methods

2.1. General design

Between 1991 and 1993, a sample of 10 593 men aged 50–60 years were included in three centres in

France: Lille in the north, Strasbourg in the east and Toulouse in the southwest, and one centre in Northern Ireland (Belfast). The sample was recruited in factories and in various firms, in occupational medicine, health screening centres and general practice (GPs' lists). Subjects were informed of the aim of the study and agreed to an annual follow-up. Approval from the appropriate local Ethical Committee was obtained in each study centre. A more detailed description of the study populations and general methodology has been reported elsewhere [19]. Briefly, in Belfast, sampling was in industry, the civil service and general practice; in Lille, approximately two-thirds of the subjects were recruited at a health screening centre, the other third from occupational medicine; in Strasbourg, sampling was principally based on one health screening centre and occupational medicine; in Toulouse, sampling was based on large industries, the civil service and several health screening centres. The sample matched broadly the social class structure of the background population [19].

Each subject completed self-administered questionnaires. These questionnaires relating to demographic, socio-economic factors and dietary habits were checked by specially trained medical staff. Additional questionnaires were administered at the clinic: information was collected on tobacco consumption, family and personal medical history, symptoms and drug intake. Baseline investigations included anthropometric measurements, a 12-lead electrocardiogram and standardized blood pressure measurements using an automatic sphygmomanometer (Spengler SP9). Venous blood samples were collected after a 10-h fast and centrifuged within 4 h. Blood samples were stored at +4°C, and were shipped at the same temperature, weekly, to the Coordinating Laboratory in Lille. All measurements were performed blind to the originating centre and by consecutive numbers, to include samples from the four centres in each analytical run. All procedures were standardized between centres.

2.2. Baseline variables

The baseline variables of PRIME included both questionnaire and clinical variables.

Questionnaire variables included parental history

of early (<65 years) MI, educational level (classified into two categories: ‘primary or intermediate school’, and ‘high school, college or university’), and lifetime smoking habit recorded in pack-years (cigarette consumption, 1 pack-year=20 cigarettes per day for 1 year).

Clinical variables were: body mass index (BMI), calculated as weight (kg)/height (m²), hypertension, defined as ‘systolic blood pressure equal to or higher than 140 mmHg’ and/or ‘diastolic blood pressure equal to or higher than 90 mm Hg’ and/or ‘use of antihypertensive medication’ [20], and diabetes mellitus, assumed if the subject currently took oral hypoglycemic therapy or insulin.

Plasma lipid analyses were conducted at SERLIA-INSERM U325 (Pasteur Institute, Lille, France). Total cholesterol and triglycerides were measured by enzymatic methods using commercial kits in an automatic analyzer (Boehringer, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein (apo) B-containing lipoproteins with phosphotungstic acid/magnesium chloride, by enzymatic method (Boehringer). Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald et al. [21]. Apo A-I and apo B were quantified by immunonephelometry (Behringwerke, Marburg, Germany). Lipoprotein(a) (Lp(a)) was measured by a two-site immunoenzymatic assay [22].

2.3. Definition of subjects’ coronary status

In order to identify histories of CAD, subjects were asked two questions: “Have you ever had any type of coronary heart disease?” and “Do you have one or more severe diseases for which you are being regularly treated or for which you have been hospitalized?” Answers were checked, using information from hospital records and family physicians (past hospitalization, acute ischemic coronary syndromes, drug intake, coronary angiography and angioplasty, coronary artery bypass graft), and diagnoses were coded using the International Classification of Diseases, 9th Revision (ICD-9) [23]. A Critical Event Committee reviewed all information and defined prevalent cases as subjects with confirmed history of acute ischemic event or stable angina. All the remaining subjects were considered as controls. These subjects had

neither acute nor stable CAD when included in The PRIME Study.

For this case-control study, subjects taking lipid-lowering drugs were excluded from statistical analyses.

2.4. Statistical analysis

Statistical analysis was performed using SAS statistical software version 6.12 (SAS Institute, Cary, USA) [24].

For categorical variables, the χ^2 and Mantel-Haenszel χ^2 tests were applied. Log-transformed data were used in statistical analyses for skewed biological variables: triglycerides and Lp(a). However, all results are expressed as arithmetic means (S.D.). Except for tobacco consumption (Wilcoxon tests), the means were compared by one- or two-way analysis of variance.

To assess the simultaneous contribution of several factors to the differences between cases and controls (primary analysis) and between Northern Irish and French controls (secondary analysis), logistic regression analyses were used. Standardized regression coefficients (odds ratio associated with one standard deviation change in the level of the risk factor) were used for continuous variables. This allows comparisons of the strength of association of the dependent variable with several risk factors, and comparison between models [25]. Testing for the significance of the difference between Northern Irish and French regression coefficients was based on the normal score test [24].

3. Results

Data from 9561 subjects were analyzed among 10 593 men. Actually, data for 1032 subjects had to be eliminated since they were on lipid-lowering drugs. There were 249 cases and 2458 controls in Northern Ireland, and 133 cases and 6721 controls in France. In Northern Ireland and in France, 56% of cases had an history of acute ischemic events.

3.1. Clinical data (Table 1)

Univariate analysis showed striking differences

Table 1

Clinical parameters in cases and controls, in Northern Ireland and France: the PRIME study^a

	Northern Ireland			France		
	Cases (n=249)	Controls (n=2458)	P	Cases (n=133)	Controls (n=6721)	P ^b
Age (years)	55.5 (2.9)	54.7 (2.9)	***	56.0 (2.7)	54.9 (2.9)	***
BMI (kg/m ²)	27.1 (3.6)	26.2 (3.4)	***	27.4 (3.8)	26.6 (3.5)	**
Hypertension (%)	55.0	41.3	***	63.9	44.7	***
Diabetes mellitus (%)	5.2	0.9	***	6.8	2.0	***
Family history of MI (%)	18.1	12.6	*	10.5	5.3	*
Tobacco consumption (pack-years)	31.8	19.5	***	26.2	15.2	***
Educational level (%):			**			ns
Primary or intermediate school	84.7	76.5		80.4	73.7	
High school, college, university	15.3	23.5		19.6	26.3	

^a BMI, body mass index; MI, myocardial infarction. For quantitative data, values are arithmetic means (S.D.).^b P adjusted for centre.

Statistical significance: *P<0.05; **P<0.01; ***P<0.001.

between cases and controls. In both countries, cases were older, were more likely to have hypertension or diabetes mellitus, and had been heavier smokers than controls ($P<0.001$). Moreover, CAD subjects had higher BMIs ($P<0.01$) and more frequently reported parental history of early MI ($P<0.05$) than controls. Educational level was significantly lower in cases than controls, but only in Northern Irish subjects ($P<0.01$).

3.2. Lipoprotein and apolipoprotein levels (Table 2)

Most biological factors associated with CAD were identical in the two countries. Mean HDL cholesterol and apo A-I concentrations were lower in cases than in control subjects, whereas levels of triglycerides

and apo B were higher in CAD than in control subjects ($P<0.05$). Total and LDL cholesterol levels did not differ between cases and controls, either in Northern Ireland, or in France. Discrepancies between biological risk factors for CAD concerned only the Lp(a) level, which was higher in cases than controls in Northern Ireland ($P<0.01$), but not in France.

3.3. Multivariate analyses

3.3.1. Logistic regression analyses between CAD and control subjects, in Northern Ireland and France (Table 3)

In both countries, factors significantly associated with CAD were age, hypertension, diabetes mellitus, tobacco consumption, and decreased HDL cholesterol

Table 2

Biological variables in cases and controls in Northern Ireland and France: the PRIME study^a

	Northern Ireland			France		
	Cases (n=249)	Controls (n=2458)	P	Cases (n=133)	Controls (n=6721)	P ^b
Total cholesterol	5.98 (1.00)	5.86 (1.01)	ns	5.71 (0.96)	5.67 (0.97)	ns
Triglycerides	2.32 (1.28)	1.98 (1.23)	***	1.78 (1.10)	1.58 (1.06)	***
HDL cholesterol	1.10 (0.34)	1.19 (0.32)	***	1.23 (0.37)	1.29 (0.34)	*
LDL cholesterol	3.84 (0.89)	3.82 (0.91)	ns	3.73 (0.86)	3.68 (0.86)	ns
Apo A-I	138.0 (24.9)	145.7 (23.7)	***	145.6 (25.5)	150.2 (25.0)	*
Apo B	144.6 (32.5)	135.5 (32.9)	***	130.2 (33.3)	124.1 (32.8)	*
Lp(a)	29.4 (38.4)	22.1 (30.5)	**	15.6 (26.6)	15.1 (22.3)	ns

^a Values are arithmetic means (S.D.), and are expressed in mmol/l for total cholesterol, triglycerides, HDL and LDL cholesterol, and in mg/dL for apo A-I, apo B and Lp(a).^b P adjusted for centre.

Statistical significance: *P<0.05; **P<0.01; ***P<0.001.

Table 3

Multivariate logistic regression analyses between cases and controls in the Northern Irish and French populations: the PRIME study^a

	Northern Ireland		France ^d		Comparison test ^c
	Cases (<i>n</i> =246)	Controls (<i>n</i> =2433)	Cases (<i>n</i> =130)	Controls (<i>n</i> =6631)	
	OR	95% CI	OR	95% CI	NS
Age ^b	1.26	1.10–1.45	1.41	1.17–1.69	NS
Education	1.37	0.95–1.97	1.32	0.84–2.07	NS
Family history of MI	1.50	1.04–2.15	1.83	0.99–3.37	NS
Hypertension	1.49	1.13–1.97	1.67	1.14–2.44	NS
Diabetes mellitus	5.42	2.53–11.60	2.24	1.06–4.73	NS
Tobacco consumption ^b	1.43	1.27–1.60	1.39	1.22–1.58	NS
HDL cholesterol ^b	0.80	0.68–0.94	0.86	0.70–1.06	NS
Triglycerides ^b	1.17	1.01–1.36	1.10	0.91–1.32	NS
Lp(a) ^b	1.22	1.06–1.40	0.96	0.81–1.15	0.01

^a OR, odds ratio; CI, confidence interval; MI, myocardial infarction.^b Standardized regression coefficients (OR associated with 1 S.D. change in the risk factor).^c Comparison of regression coefficients by normal score test.^d Regression including centres (Lille, Strasbourg, Toulouse) as a covariable.

(NS in France) or apo A-I levels (odds ratio (OR)=0.74 (0.63–0.85) and OR=0.82 (0.67–0.99) in Northern Ireland and France, respectively). Discrepancies between Northern Irish and French models concerned only a few variables: parental history of early MI and a rise in triglycerides or Lp(a) level, which were associated with a higher prevalence of CAD in Northern Ireland, but not in France. Moreover, the odds ratios of the risk factors associated with CAD in both countries were generally of the same order of magnitude. As shown by the comparison test, the strength of the associations with CAD was similar, except for Lp(a) (Table 3).

3.3.2. Comparisons between Northern Irish and French control subjects (Table 4)

To analyze more thoroughly the risk profiles of the Northern Irish and French populations, logistic regression analyses were conducted between the control subjects of the two countries. The results showed that the Northern Irish population was not characterized by higher prevalences of all clinical risk factors for CAD, since hypertension, diabetes mellitus and higher BMIs were more frequent in French control subjects. On the other hand, the lipid profile of Northern Irish subjects was clearly worse than the French one, combining elevation of triglycerides, LDL, apo B and Lp(a) levels, and reduction of HDL cholesterol or apo A-I levels (OR=0.87 (0.82–0.92)).

4. Discussion

The large differences in incidence and mortality for CAD between countries have been widely documented [5,26]. At least two hypotheses can be put forward to explain this ‘intercountry’ variability: the incidence of CAD might essentially depend on the prevalence of cardiovascular risk factors in the population, or it might also be determined by the strength of the associations between cardiovascular risk factors and CAD in countries [16,17].

Table 4

Multivariate logistic regression analyses between Northern Irish (*n*=2462) and French controls (*n*=6649): the PRIME study^a

	OR ^c	95% CI
BMI ^b	0.72***	0.68–0.77
Hypertension	0.85**	0.77–0.95
Diabetes mellitus	0.41***	0.25–0.68
Family history of MI	2.57***	2.16–3.05
Tobacco consumption ^b	1.16***	1.10–1.21
Educational level	0.84**	0.74–0.94
Triglycerides ^b	1.63***	1.54–1.73
HDL cholesterol ^b	0.83***	0.78–0.88
LDL cholesterol ^b	1.06*	1.01–1.11
Lp(a) ^b	1.29***	1.23–1.36

^a CI, confidence interval; OR, odds ratio; BMI, body mass index; MI, myocardial infarction.^b Standardized regression coefficients (odds ratio associated with 1 S.D. change in the risk factor).^c Odds ratio higher/lower than 1 means that Northern Irish controls have a higher/lesser frequency or mean value than French controls.Statistical significance: ns, not significant **P*<0.05; ***P*<0.01; ****P*<0.001.

Numerous studies have focused on the relationships between conventional risk factors and CAD, in several populations and in many countries [5,7,13,14,27]. Interestingly, they have often led to conflicting results. But these discrepancies cannot be regarded as a reliable answer to the question of the contrasted populations' susceptibilities to risk. In the various studies, large variations exist in the characteristics of the populations, but also in the definition of coronary events or risk variables, and even in the methodological approach. So, it remains difficult to assess whether discrepancies reflect actual differences between countries. Only international and multicentre studies designed for this purpose may clarify this question, using a single data set and standardized procedures. However, such studies remain uncommon, especially those involving European adults from countries at contrasting risk for CAD. Hence, the main purpose of this work was to compare the associations between conventional cardiovascular risk factors for CAD and coronary status of middle-aged men, in Northern Ireland and France.

Our results firstly confirmed the well-known higher prevalence of CAD in Northern Ireland than in France [26,27]. Secondly, the analysis showed a large similarity between Northern Irish and French models of CAD risk. CAD was more frequent in subjects who were older, heavier smokers, hypertensive, diabetic, or with decreased serum HDL cholesterol or Apo A-I levels. Moreover, for most of these risk factors, except for Lp(a), the association with coronary status was of the same order of magnitude in the two countries. These results would tend to suggest that many classical risk factors for CAD are identical in Northern Irish and French subjects, but also that the susceptibility of the two populations to risk is equivalent.

For some variables, the similarity of odds ratios between Northern Ireland and French logistic models, was not obvious. These discrepancies might firstly reflect imprecision in the definition of the variables, rather than actual differences between countries. For example, in our study, subjects were defined as diabetic if they currently took oral hypoglycemic drugs or insulin. Therefore, the odds ratios calculated for this variable represent the strength of the association between the presence of hypoglycemic therapy and CAD in each country, and not specifically the

association between diabetes and CAD. The odds ratios were thus largely dependent on practitioners' prescription patterns, which differ highly in the two countries [28–30]. Another difference between Northern Irish and French logistic models concerned the parental history of early MI [14,31], which was significantly associated with a higher prevalence of CAD in Northern Ireland, but not in France. The higher prevalence of a family history of MI and the difference in the number of CAD events might explain this contrast between Northern Irish and French logistic models.

Two major differences emerged in lipid variables between the countries: whereas reverse cholesterol transport related variables were associated with CAD in both, the relationship between triglycerides or Lp(a) and the subjects' coronary status was only verified in Northern Ireland. The inverse relation of HDL (or Apo A-I) levels and the development of CAD is now accepted [32]. Conversely, with standardized procedures, the same statistical methodology has led to conflicting conclusions about triglycerides and Lp(a) associations with CAD, depending on whether the Northern Ireland or French populations were studied. Lp(a) is a lipoprotein whose level is largely determined by genetic factors [12,33–37]. Undoubtedly, increased Lp(a) level adds to the risk of CAD [14,38]. But this relation seems rather population or racially dependent, since several studies have failed to identify Lp(a) as an independent risk factor [11,13]. Furthermore, recent studies have suggested that the risk of CAD associated with elevated Lp(a) level may be restricted to subjects with a high plasma total cholesterol level or with an increased total/HDL cholesterol ratio [39,40]. Our results tend to confirm these findings, as Lp(a) appeared as an independent risk factor for CAD only in Northern Irish subjects, who also had lower HDL cholesterol levels. However, to assert the difference of susceptibility for Lp(a) between Northern Ireland and France, the prospective part of the PRIME study is required. Likewise, increased triglycerides level appeared as an independent risk factor for CAD in Northern Irish subjects. However, the role of triglycerides as an independent risk factor in CAD remains controversial [41].

The higher prevalence of CAD in Northern Ireland than in France might thus be explained by a greater

prevalence of risk factors in Northern Ireland. The results of the logistic regression analyses indicated that apolipoprotein, lipoprotein and lipid risk factors studied were more prevalent in Northern Irish than in French control subjects. These differences could thus explain partially the different CAD prevalence between Northern Ireland and France. Our previous work [19] and our present data suggest that triglycerides, Lp(a) and HDL cholesterol but also new risk factors remain to be investigated to explain the large difference in CAD prevalence and incidence in Northern Ireland and in France. Differences in the genetic background between the two populations and genetic/environmental interactions need also to be further elucidated.

In conclusion, these first results indicate that, except for Lp(a), there are no major differences in the susceptibility to conventional risk factors for CAD between neighboring countries at contrasted risk. Results also tend to suggest that the higher prevalence of CAD in Northern Ireland might partially depend on the unfavourable lipid profile of its middle-aged men.

Acknowledgements

The PRIME Study is organized under an agreement between INSERM and the Merck, Sharpe and Dohme-Chibret Laboratory, with the following participating Laboratories: (1) The Strasbourg MONICA Project, Department of Epidemiology and Public Health, Faculty of Medicine, Strasbourg, France (D. Arveiler, B. Haas). (2) The Toulouse MONICA Project, INSERM U518, Toulouse, France (J. Ferrières, JB. Ruidavets). (3) The Lille MONICA Project, INSERM U508, Lille, France (P. Amouyel, M. Montaye). (4) The Department of Epidemiology and Public Health, The Queen's University of Belfast, Belfast, Northern Ireland, UK (A. Evans, J. Yarnell). (5) The Department of Atherosclerosis, SERLIA-INSERM U325, Lille, France (G. Luc, JM. Bard). (6) The Laboratory of Hæmatology, La Timone Hospital, Marseille, France (I. Juhan-Vague). (7) The Laboratory of Endocrinology, INSERM U326, Toulouse, France (B. Perret). (8) The Vitamin Research Unit, The University of Bern, Bern, Switzerland (F. Gey). (9) The Trace Element Laboratory, Department of

Medicine, The Queen's University, Belfast, Northern Ireland, UK (D. McMaster). (10) The DNA Bank, Service Commun n°7 INSERM, Paris, France (F. Cambien). (11) The Coordinating Center, U258 INSERM, Paris, France (P. Ducimetière, PY. Scarabin, A. Bingham).

We thank the following organisations which allowed the recruitment of the PRIME subjects: the Health screening centres organized by the Social Security of Lille (Institut Pasteur), Strasbourg, Toulouse and Tourcoing; Occupational Medicine Services of Haute-Garonne, of the Urban Community of Strasbourg; the Association Inter-entreprises des Services Médicaux du Travail de Lille et environs; the Comité pour le Développement de la Médecine du Travail; the Mutuelle Générale des PTT du Bas-Rhin; the Laboratoire d'Analyses de l'Institut de Chimie Biologique de la Faculté de Médecine de Strasbourg. Grant support: The PRIME Study is supported by grants from Merck, Sharp & Dohme-Chibret.

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