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Effects of insulin-like growth factor 1 in preventing acute coronary syndromes: The PRIME study

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ABSTRACT

Objective: Insulin-like growth factor-1 (IGF-1) has been associated with cardiovascular risk factors and atherosclerosis. The aim of the present study was to evaluate the prognostic value of IGF-1 concentrations with respect to occurrence of well-defined coronary syndromes.
Methods: The PRIME study is a prospective cohort having included 10,600 subjects from Northern Ireland and France. Detailed information on cardiovascular risk factors, socioeconomic and behavioural variables were collected and a cardiologic examination was performed. At 5-year follow-up, 317 incident cases of coronary events were recorded according to strict protocols. They were matched to 634 age- and centre-paired controls from the same cohort, free of coronary disease. Baseline IGF-1 concentrations were measured, together with variables of lipid and glucose metabolism and markers of vascular and systemic inflammation.
Results: Baseline IGF-1 concentration was lower in subjects developing an acute coronary syndrome than in unaffected controls. IGF-1 levels correlated negatively with age, waist circumference, tobacco consumption and markers of inflammation. Subjects in the highest quartile of IGF-1 distribution had a 55% reduction in the relative risk of developing myocardial infarction and a 45% decrease for all-combined acute coronary syndromes. A similar trend, although non-significant, was noted for angina pectoris. Multiple adjustments on classical risk factors and inflammation markers did not affect IGF-1 results. Elevated levels of both IGF-1 and apo A-I conferred a significantly greater risk reduction than either one alone. However, interaction between the two markers was not significant.
Conclusion: Like HDL markers, high levels of IGF-1 confer protection against coronary artery disease.

1. Introduction

Insulin-like growth factor-1 concentrations have been related to cardiovascular diseases and impaired glucose tolerance [1–3]. Various epidemiological studies, particularly in elderly people, have reported that a low IGF-1 level is associated with high blood pressure, carotid atherosclerosis and cardiovascular mortality [1,4–6]. In the present study, the first objective was to re-evaluate the relationship between IGF-1 and occurrence of well-defined acute coronary syndromes, in PRIME, a population-based prospective study [7] at 5-year follow-up. Furthermore, a low IGF-1 might predispose to metabolic syndrome, visceral obesity and type-2 diabetes [8,9]. Both atherosclerosis and insulin resistance are characterized by a chronic low-grade inflammatory state [10]. Endothelial dysfunction, triggered by hemodynamic conditions, pro-inflammatory cytokines and oxidized lipoproteins promotes leukocyte transmigration through vascular wall, which is an early

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event in atherogenesis [11]. Recent studies suggest that IGF-1 exerts anti-inflammatory properties, through decreasing expression of pro-inflammatory cytokines [12]. Conversely, interleukin-6 would decrease IGF-1 levels [13]. This suggests that beneficial effects of IGF-1 would be mediated through control of inflammatory processes.

In the present study, the relationship between IGF-1 and coronary artery disease was examined with particular attention to the inflammatory status and to markers of endothelial dysfunction.

2. Patients and methods

Cohort recruitment and examination methods have been previously described [7] and only the main features are reminded.

2.1. Population recruitment

The PRIME study (Prospective Epidemiological Study of Myocardial Infarction) was established in 1991, involving four collaborating WHO-MONICA centres in Belfast (UK), Lille, Strasbourg and Toulouse (France). The target was to recruit 2500 men in each centre, aged 50–59 years, and to follow them for a minimum of 5 years. Recruitment frame was based on various industry and employment groups, on health screening centres and general practice. Participants gave informed written consent. They were given a morning appointment and asked to fast for at least 12 h.

2.2. Personal history and examination

Self-administered questionnaires related to personal and family history, demographic and socioeconomic factors, diet, tobacco and alcohol consumptions, drug intake and physical activity were completed at home by the participants and checked by a clinical investigation technician. The questionnaire on personal medical history was completed together with the Rose Questionnaire for chest pain and possible infarction [14], and a standard 12-lead electrocardiogram was recorded. Anthropometric measurements were performed and blood pressure was determined on two occasions in the sitting position.

Subjects were considered free of coronary disease at entry if no criterion among the following three was met: [1] reported myocardial infarction and/or angina pectoris diagnosed by a physician [2], electrocardiographic evidence of myocardial infarction defined as major or moderate Q waves coded using the Minnesota system [15,3] a positive answer to the Rose Questionnaire.

2.3. Follow-up

Subjects were annually contacted by letter and asked to complete a clinical event questionnaire to be returned to the centre. If the subject did not comply, phone contact was established with him or his general practitioner. For all subjects reporting a possible event, clinical information was sought directly from the hospital or general practitioner notes. All details of electrocardiograms, hospital admissions, blood enzymes, surgical operations, angioplasty and treatments were collected. Death certificates were checked to support clinical and post-mortem information on causes of death. A Medical Committee was established, including one member from each PRIME Centre, and three independent cardiologists who assigned a code for each case according to a strict protocol.

Myocardial infarction was defined by one of the following conditions: new diagnosed Q wave or other fresh typical electrocardiographic signs of necrosis, typical or atypical pain symptoms and new electrocardiographic ischemia and myocardial enzyme levels over twice upper limits, post-mortem evidence of fresh myocardial infarction or thrombosis. *Definite coronary death* was defined as death with a documented coronary event. Sudden death was defined as unexplained death occurring within 1 h following symptoms. However, when significant coronary atheroma was present at autopsy, it was also considered as definite coronary death. When coronary death was suspected, with no other documentation or explanation, it was labelled possible coronary death. The three categories were grouped as coronary deaths. *Hard coronary cases* were subjects who had at least one non-fatal myocardial infarction event or who died from coronary disease during follow-up. *Angina pectoris* was defined by the presence of chest pain at rest and/or on exertion and one of the following criteria: angiographic stenosis over 50% or a positive scintigraphy or positive exercise stress test or electrocardiogram changes at rest but with neither myocardial infarction nor evidence of a non-coronary cause in the clinical history. *Total coronary cases* were defined as all subjects with at least one of the categories of coronary death, non-fatal myocardial infarction or angina pectoris.

2.4. Nested case–control study

After 5 years follow-up of the PRIME cohort, a nested case–control study was constructed: for each incident CHD event occurring during follow-up, two controls were randomly selected from the participants in the PRIME cohort who had remained free of CHD over the same period. Controls were matched for age (±3 years), recruitment centre and examination date (±3 days).

2.5. Biological measurements

Biological parameters were assayed in sera collected at baseline of PRIME and were measured in different French central laboratories. Plasma samples were shipped in dry ice from the central plasma bank in Lille to each laboratory. For all parameters, measurements were carried out as batch analyses. Highly sensitive CRP was measured by immuno-nephelometry (hs-CRP: Dade Behring), IL-6 by an ELISA assay (R&D Systems) as were ICAM-1 and VCAM-1 (Immunotech, Beckman Coulter). Fibrinogen was determined according to Clauss [16]. Insulin was assayed by a competitive radioimmunoassay (Sanofi-Diagnostic Pasteur) cross-reacting with pro-insulin. Accuracy and precision were assured by a strict internal quality control program, using either quality controls from the supplier (CRP, insulin) or a single batch of normal plasma pooled from 50 healthy subjects. The coefficients of variation were 4.4%, 7.8%, and 4.3% for CRP, IL-6, and fibrinogen, respectively, 5% for insulin and 12% and 9% for ICAM-1 and VCAM-1, respectively. Laboratory staff was unaware of case or control status.

Plasma lipids were measured in a centralized laboratory on entry as previously described [17]. LDL cholesterol was calculated according to the Friedewald's formula and subjects with triglycerides over 4 g/L were excluded from analysis. Glucose was assayed by the glucose oxidase technique.

Plasma IGF-1 was measured using a two-site immunoenzymometric assay, including a sample pre-treatment to avoid interference from binding proteins (ImmunoDiagnostic Systems, Paris). Intra- and inter-assay coefficients of variations ranged between 5 and 7%.

2.6. Statistical analyses

Continuous and qualitative variables are presented as arithmetic means and percentages, respectively, with 95% confidence intervals. Variables with a skewed distribution including triglycerides, VCAM-1, CRP and HOMA-IR index were log transformed and presented as geometric means. Insulin, alcohol and tobacco consumptions were presented as medians with inter-quartile ranges. Baseline characteristics between case–control pairs were

Table 1
Baseline characteristics (mean, percentage, 95% CI or median) of study participants: the PRIME study.

	Controls (n = 588)	Cases (n = 294)	p
Age (years)	55.2 55.1–55.3	55.3 55.2–55.5	0.09
Education (years)	10.9 10.7–11.2	10.8 10.4–11.2	0.54
Treatment for			
Diabetes mellitus (%)	1.4 0.3–2.5	3.5 2.0–5.0	0.04
Hypertension (%)	10.7 7.7–13.7	20.3 16.2–24.3	0.001
Dyslipidemia (%)	4.9 2.9–7.0	10.5 7.7–13.3	0.003
Physical activity (%)	90.1 87.5–92.6	88.7 85.6–92.2	0.54
Alcohol consumption (g/d)	18.8 3.6–42.2	17.6 0.0–36.8	0.17**
Smoking (pack year)	15.7 0.0–32.9	23.0 3.3–42.6	0.001**
Body mass index (kg/m^2)	26.6 26.3–26.9	27.2 26.8–27.6	0.02
Waist circumference (cm)	93.8 93.0–94.6	95.7 94.6–96.7	0.02
Systolic blood pressure (mm Hg)	134 132–135	140 138–142	0.001
Blood measurements			
Triglycerides (g/L)	1.36 1.30–1.42	1.49 1.41–1.58	0.03*
Total cholesterol (g/L)	2.24 2.20–2.27	2.34 2.29–2.38	0.001
HDL cholesterol (g/L)	0.47 0.46–0.49	0.44 0.43–0.46	0.001
Apolipoprotein A-I (g/L)	1.48 1.46–1.50	1.40 1.37–1.42	0.001
Apolipoprotein B (g/L)	1.30 1.27–1.33	1.42 1.38–1.46	0.001
Blood glucose (mmol/L)	5.31 5.18–5.43	5.58 5.41–5.74	0.02
Insulin (μIU/mL)	9.2 0.0–14.0	9.5 6.6–16.0	0.14**
HOMA-IR index	2.95 2.75–3.17	3.18 2.92–3.47	0.21*
ICAM-1 (ng/mL)	593 576–609	648 627–670	0.001
VCAM-1 (ng/mL)	780 762–799	797 771–823	0.33*
CRP (mg/L)	1.3 1.2–1.5	1.9 1.7–2.2	0.001*
Fibrinogen (mg/dL)	3.35 3.27–3.43	3.60 3.49–3.70	0.001
IGF-1 (μg/L)	37.3 36.2–38.4	35.2 33.7–36.8	0.03

* Log transformed data (geometric mean).
** Median, interquartile range.

compared. In the control group, associations of IGF-1 with anthropometric and clinical characteristics, metabolic parameters and inflammatory markers were tested using Spearman rank correlations. The method of Benjamini and Hochberg was used to correct for multiple tests in baseline characteristic comparisons between controls and cases.

To assess the shape of the relationship between IGF-1 and CHD risk, subjects were grouped according to quartiles of its distribution. Hazard ratios of CHD for each quartile relative to the lowest one were estimated by conditional logistic regression analysis. The 'optimal' cut-off point of IGF-1 was determined through the maximization of the Youden index [18]. The 75th percentile (43.6 μg/L) corresponded to the optimal cut-off value. HRs were estimated using conditional logistic regression analysis, successively without and with adjustment for demographic data (age and education) and classic CHD risk factors. Further adjustments for CRP, ICAM-1, fibrinogen, glycaemia and insulin were also performed. Interaction effect between IGF-1 and apo A-I was tested using stratification of apo A-I from both sides of the median and cut-off of quartile Q3–Q4 for IGF-1. Estimated hazard ratios are presented with 95% confidence intervals. Analyses were two-sided and $p < 0.05$ was considered to be significant. All computations were carried out with SAS software, version 9.2 (SAS Institute, Cary, IL, USA).

3. Results

In the frame of the population-based PRIME cohort, 10 600 subjects from Northern Ireland and France were followed up. After 5 years, 317 incident coronary events were recorded: 120 from Belfast (out of 2399 free of coronary disease at entry) and 197 from France (out of 7359). Annual incidence rates for all coronary events per 1000 participants with their 95% confidence intervals, were 10.5 (8.6–13.7) and 5.5 (4.7–6.2) in Belfast and French centres, respectively. Among incident coronary events, 48.6% presented

Table 2
Spearman rank correlation coefficients and *p* values between baseline IGF-1 and clinical and biological variables in the control subjects of the PRIME study.

Variables	Correlation coefficient	*p*
Age (years)	−0.11	0.02
Smoking (pack year)	−0.14	0.001
Alcohol consumption (g/d)	−0.02	0.70
Waist circumference (cm)	−0.10	0.02
Body mass index (kg/m^2)	−0.05	0.22
Systolic blood pressure (mm Hg)	−0.06	0.12
Blood glucose (mmol/L)	−0.08	0.08
Insulin (μIU/mL)	0.02	0.64
CRP (mg/L)	−0.16	0.001
Fibrinogen (mg/dL)	−0.02	0.66
ICAM-1 (ng/mL)	−0.08	0.04
VCAM-1 (ng/mL)	−0.02	0.64
Total cholesterol (g/L)	0.04	0.31
HDL-cholesterol (g/L)	0.04	0.38
Triglycerides (g/L)	0.03	0.51
Apolipoprotein B (g/L)	0.04	0.40
Apolipoprotein A-I (g/L)	0.07	0.10

with angina and 51.4% with MI. Fatal MI represented 19.8% of myocardial infarction patients and 10.4% of all coronary events. These latter proportions were not very different between French (10.6) and Northern-Ireland (10.0) recruitment centres.

A nested-case control study was built in the frame of PRIME. Globally, cardiovascular risk factors were much more prevalent in cases (Table 1). Proportions of patients treated for dyslipidemias, hypertension or diabetes were ≥2-fold higher in cases than in controls. Concordantly, systolic blood pressure, apo B (protein marker of LDL-cholesterol), glycaemia and the HOMA index for insulin resistance were increased, as were cigarette and alcohol consumptions. Parameters of vascular (ICAM-1 and VCAM-1) or systemic (CRP and fibrinogen) inflammation were also higher in cases than in controls. Identical observations were made for interleukin-6 (not shown). Conversely, levels of IGF-1 and of apo A-I (marker of HDL-cholesterol) were significantly lower in cases than in controls.

We first investigated correlations between IGF-1 and clinical or biological variables among control subjects (Table 2) since cases belonged to a very specific sub-population with a high proportion of men under therapy at baseline for diabetes, hypertension or dyslipidemia (27.8%, the double than in controls). As expected, IGF-1 concentration was inversely related with age ($p = 0.02$). Inverse correlations were also found with smoking habits, waist circumference, CRP and ICAM-1 ($p \leq 0.04$). A trend to a positive relation with apo A-I was noted ($p = 0.10$). All those correlations will be considered for further statistical analyses and adjustments.

We then calculated the relative risk (HR) of developing an ACS as a function of IGF-1 levels, divided in quartiles of the whole population (Table 3). Interestingly, IGF-1 in the 4th quartile was associated with a 50% reduction of all coronary events. There was no difference in relative risk for the 3 other quartiles. The inter-quartiles trend was significant for combined ACS, and close to significance for MI. In all further analyses, comparisons will be performed between quartile 4 and the 3 first ones.

Multivariate analyses were performed taking into account different groups of confounding variables (Table 4). Crude analysis (model 1) showed that quartile 4 of IGF-1 distribution (>43.7 μg/L) was associated with a 50% reduction in the HR for all-combined ACS and for MI. A similar trend was recorded for angina pectoris but did not reach statistical significance ($p = 0.08$). A first adjustment was made on age and on variables associated to major cardiovascular risk factors: treatments for dyslipidemias, hypertension, diabetes, levels of apolipoproteins, blood pressure, alcohol and tobacco consumptions, waist circumference, and physical activity (model 2). In the subsequent models, further adjustments were made on variables associated with insulin resistance (glycaemia and insulin) and on parameters of inflammation (CRP, fibrinogen, and ICAM-1). After all adjustments, the same information as in the crude analysis was confirmed, indicating that high IGF-1 was protective against occurrence of MI and of all-combined ACS. Intermediate models with adjustments on risk factors plus insulin/glycaemia, or on inflammation markers alone yielded similar results (not shown).

Table 3
Hazard ratios for combined acute coronary syndromes (ACS), myocardial infarction (MI) or angina pectoris, according to quartiles of IGF-1 baseline plasma concentration (μg/L) in apparently healthy men included in the PRIME study.

	Q1 <25.0	Q2 25.0–32.7	Q3 32.8–43.7	Q4 >43.7	*p* for trend
ACS	(*n* = 216)	(*n* = 222)	(*n* = 220)	(*n* = 218)	
	1	1.04	1.08	0.53	0.04
		0.70–1.55	0.71–1.65	0.33–0.85	
MI	(*n* = 116)	(*n* = 114)	(*n* = 115)	(*n* = 105)	
	1	1.21	1.04	0.45	0.07
		0.70–2.11	0.60–1.81	0.23–0.90	
Angina	(*n* = 103)	(*n* = 115)	(*n* = 108)	(*n* = 114)	
	1	0.78	0.96	0.55	0.15
		0.44–1.37	0.51–1.81	0.29–1.06	

Unadjusted hazard ratios.

Contrary to classical risk factors, positively related to coronary artery disease, HDL exerts athero-protective effects. We next investigated possible interaction effect of apo A-I and IGF-1 in cardiovascular risk protection. Apo A-I was considered from both sides of the median (1.41 g/L) and IGF-1 around the Q4 cut-off (43.7 μg/L). A terms of interaction between IGF-1 and apo A-I was introduced in each multivariate model. Tested Interactions were not significant in any model. As a reference, we considered the situation where both markers were below those respective thresholds. In the presence of IGF-1 below Q4 (≤43.7 μg/L), a high apo A-I level (>1.41 g/L apo A-I) conferred a significant risk reduction for MI: HR was 0.44 (0.23–0.83). However, combination of elevated levels of both IGF-I (>43.7 μg/L) and apo A-I (>1.41 g/L) yielded greater reductions in the risk for MI: HR was 0.14 (0.05–0.41) (not shown). Differences (paired comparisons) were statistically significant comparing this latter situation to those in which only one of those two markers was elevated (not shown). Similar trends, although of lesser magnitude and not reaching statistical significance, were observed for angina pectoris. A terms of interaction between IGF-1 and apo A-I was introduced in each multivariate model. Tested interactions were not significant in any model.

Table 4
Hazard ratios for combined acute coronary syndromes (ACS), myocardial infarction (MI) or angina pectoris, according to IGF-1 baseline plasma concentration (quartile 4 vs the 3 first ones) in apparently healthy men included in the PRIME study.

	Model 1 IGF-1 >43.7 vs ≤43.7 μg/L	Model 2 IGF-1 >43.7 vs ≤43.7 μg/L	Model 3 IGF-1 >43.7 vs ≤43.7 μg/L
ACS	0.51	0.57	0.58
	0.34–0.78	0.36–0.89	0.35–0.84
	0.002	0.02	0.03
MI	0.42	0.42	0.44
	0.23–0.77	0.21–0.84	0.21–0.95
	0.005	0.02	0.04
Angina	0.60	0.64	0.58
	0.34–1.06	0.35–1.18	0.30–1.15
	0.08	0.16	0.12

Model 1: crude analysis (unadjusted).
Model 2: adjusted on age, treatment for diabetes, hypertension, dyslipidemia, tobacco and alcohol consumptions, levels of physical activity and education, waist circumference, systolic blood pressure, apolipoproteins A-I and B.
Model 3: further adjustments on CRP, ICAM-1, fibrinogen, glycaemia and insulin.

4. Discussion

In the present study, high IGF-1 level appears as a negative, independent predictor of occurrence of acute coronary syndromes at 5 years.

Numerous observational, mostly cross-sectional, studies have reported associations between IGF-1 and blood pressure, cardiovascular events, or pre-clinical atherosclerosis, as documented by the presence of carotid atherosclerotic plaques or by intima/media thickness [1,4,8]. However, the GH/IGF-1 axis declines with age with a large variability between individuals, emphasizing the need for prospective studies. Several such studies have been conducted, particularly among elderly people, showing that low IGF-1 is predictive of all-cause and cardiovascular mortality [2,19]. Recently, a bioassay was devised to specifically measure unbound bioactive IGF-1 and elevated IGF-1 bioactivity was found predictive of extended survival among elderly [6]. All those observations seem consistent, yet a more complex relationship, following a U-shaped pattern, between IGF-1 and cardiovascular mortality in elderly has been reported [3,5]. A similar ambivalence has been described concerning a possible relationship between IGF-1 and congestive heart failure [3,20].

This prompted us to re-examine the predictive potential of IGF-1 with respect to occurrence of well-defined coronary syndromes in healthy middle-aged adults. In the WHO MONICA Project [21], the ratio of incident myocardial infarction and coronary death rates between Northern-Ireland and France was estimated at around 3. Due to an important reduction of coronary disease rates during the 1990s, especially in Northern-Ireland, this ratio was only 1.92 (95% CI, 1.52–2.42) in PRIME after five years follow-up. Cases distributed almost equally between angina pectoris and myocardial infarction. Elevated IGF-1 was predictor of MI, and a weaker, non-significant, trend was recorded for angina. This difference suggests that IGF-1 might exert a protective effect towards occurrence of a thrombotic event, rather than on the development of the atherosclerosis process. Thus, IGF-1 might be involved in the late phases of plaque denudation and destabilization.

Inflammation is a key process in the development of atherosclerosis both for early lesions and further, during plaque rupture. IGF-1 can temper expression of pro-inflammatory cytokines [12,22]. Interestingly, the protective effect of IGF-1 was found independent of inflammatory markers, either systemic (CRP, fibrinogen) or local (ICAM-1). Other adjustments on IL-6 or VCAM did not modify the association (not shown). This suggests that major effects of IGF-1 are independent of inflammation control.

HDL is so far considered as the sole protective factor against atherosclerosis, promoting the reverse cholesterol transport between peripheral cells and the liver. However, HDL also acts in the vascular wall, displaying anti-oxidant and anti-inflammatory properties and favouring endothelial cell repair [23,24]. Interestingly, combination of high levels of IGF-1 (higher than fourth quartile) and of apo A-I (higher than median), the major protein marker of HDL, resulted in a strong reduction (−85%) of MI occurrence, of higher magnitude than increased levels of either marker alone. Comparable results were obtained when HDL-C was considered instead of apo A-I (not shown). This suggests possible collaborative effects of IGF-1 and HDL in risk prevention. However, the two variables probably act independently, since our results on IGF-1 were always adjusted on risk factors (including apo A-I), and since no statistical interaction was observed between them.

Interventional trials in GH-deficient patients have brought some clues regarding the effects of the GH/IGF-1 axis on the vasculature. In those patients, an increased IMT has for long been recorded [25]. Treatment with GH normalizes IMT, and also improves flow-mediated endothelium-dependent vasodilatation [26]. When administered to healthy volunteers, GH increases the number of circulating endothelial progenitor cells (EPCs) and stimulates production of nitric oxide, a major mediator of endothelial functions [27]. EPCs are derived from bone marrow and are mobilized in the circulation, where they participate to endothelial repair. EPCs decline with age and a possible effect of IGF-1 would be to restore EPC number and functions, thus contributing to maintain endothelium integrity [28]. A recent population-based study has demonstrated that low IGF-1 was associated with impaired endothelial function in males [29]. On the other hand, different studies have established that HDL promotes endothelial cell proliferation and survival, and nitric oxide biosynthesis [23,30]. Thus, we may hypothesize that IGF-1 and HDL cooperate to favour endothelial integrity and repair.

Although the PRIME study offers the opportunity to examine the relationship between IGF-1 and well-defined ACS in a prospective setting, it has also its own limitations. PRIME investigates a very homogeneous population of men aged 50–59 years at baseline making difficult to transpose the results to other populations, other age groups or women. Specific to the present study, measurements of IGF-binding proteins were not available. However levels of IGF-1 and IGF-BP1 or BP3 are strongly correlated and, in previous works, their associations with mortality or cardiovascular disease were similar to those displayed by IGF-1 [1,2].

5. Conclusion

This case–control study, nested within a large prospective cohort, supports the view that IGF-1 can be considered, like HDL, as an independent negative predictor of acute coronary syndromes. Further studies are required to elucidate the mechanisms responsible of this anti-thrombotic effect of IGF-1.

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Appendix A. The PRIME study group

The PRIME study is organized under an agreement between INSERM and the Merck, Sharpe and Dohme-Chibret Laboratory, with the following participating laboratories:

- The Strasbourg MONICA Project, Laboratoire d'Epidémiologie et de Sante Publique, EA 3430, Strasbourg, F-67085, France and Université de Strasbourg, Strasbourg, F-67085, France (D. Arveiler, B. Haas),
- The Toulouse MONICA Project, INSERM U558 and Department of Epidemiology, Université Paul Sabatier – Toulouse Purpan, Toulouse, France (J. Ferrières, J-B. Ruidavets),
- The Lille MONICA Project, INSERM U744, Lille, France; Institut Pasteur de Lille, Lille, France; and Université Lille Nord de France, Lille, France (P. Amouyel, M. Montaye),
- The Department of Epidemiology and Public Health, Queen's University, Belfast, Northern Ireland (A. Evans, J. Yarnell, F. Kee),
- The Department of Atherosclerosis, INSERM, U545, Lille; Institut Pasteur de Lille, Lille; and Faculté de Médecine, and Université Lille Nord de France, Lille, France (G. Luc, J.-M. Bard),
- The Laboratory of Haematology, INSERM, U626, Marseille, Hôpital La Timone, Marseille, France (I. Juhan-Vague, P. Morange),
- The Laboratory of Endocrinology, INSERM U1048, Toulouse, France (B. Perret),
- The Vitamin Research Unit, The University of Bern, Bern, Switzerland (F. Gey),

- The Nutrition and Metabolism Group, Centre for Public Health, Queen's University Belfast, Northern-Ireland (J. Woodside, I. Young),
- The DNA Bank, INSERM/UPMC, Paris Universitas UMRS 937, Paris, F-75013 (F. Cambien),
- The Coordinating Centre, IFR 69, Villejuif, F-94807, France (P. Ducimetière),
- INSERM U970, Villejuif, F-94807, France and University Paris V, Paris Cardiovascular Research Centre (PAARC), Paris, F-75015, France (A. Bingham).

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