South-to-North gradient in lipid peroxidation in men with stable coronary artery disease in Europe

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Aims A South-to-North gradient across Europe exists for the incidence of coronary artery disease (CAD) rates. Low-density lipoprotein (LDL) oxidation is a hallmark of atherosclerosis and CAD development. The aim of our study was to determine whether differences exist in the degree of LDL oxidation in stable CAD patients from different regions of Europe.

Methods and results A cross-sectional multicentre study included 790 stable CAD male subjects aged 35–79 years (61.4 ± 9.5) from six European countries in three regions by latitude: Northern (Finland and Sweden), Central (Germany), and Southern (Greece, Spain, and Italy). Plasma oxidized LDL (oxLDL) levels were determined. Alcohol intake and lipid profile were significantly associated with oxLDL. The Italian participants had the highest oxLDL levels. A sensitivity analysis showed the models yielded higher adjusted oxLDL values in Northern (63.8 U/L) than in Central (57.6 U/L) and Southern populations (56.5 U/L), P < 0.001, after excluding Italian subjects. The probability of Southern Europe scoring the lowest oxLDL levels was >71% in all fitted models.

Conclusion Our findings suggest a gradient in LDL oxidation from Southern to Northern Europe that consistently holds for all levels of LDL, except for Italy; this country displays the highest levels in Europe, for unknown reasons.

KEYWORDS Atherosclerosis; Lipid peroxidation; Oxidative stress; Epidemiology; Coronary artery disease

The roster of AIRGENE Investigators is available at www.regicor.org/airgene_inv

Introduction

Atherosclerosis is a multifactorial process and coronary artery disease (CAD) is one of its most important manifestations. CAD is largely responsible for population mortality and morbidity in developed countries but substantial differences in incidence and mortality rates exist among countries.1 In particular, low mortality rates have been observed together with high prevalence of coronary risk factors in the Mediterranean countries of Southern Europe.2,3 This suggests that the amount of total cholesterol and/or low-density lipoprotein (LDL) cholesterol may not be the only important lipid determinant of CAD risk. Oxidized or modified LDL is assumed to be more damaging to the arterial wall than native LDL.4

High oxidative stress results in lipoprotein phospholipids becoming progressively oxidized. Free radicals cross-link and change the conformation of the apolipoprotein B molecule of LDL, resulting in a particle known as oxidized LDL (oxLDL).5 Its presence in plasma and in atherosclerotic lesions has been strongly associated with CAD, acute coronary syndromes, and vulnerable plaques.6–10 The balance between free radical generation and antioxidant defence determines the amount of circulating oxLDL. Antioxidants in the traditional Mediterranean diet may contribute to the attenuation of atherosclerosis11 by protecting LDL against oxidation. Ageing,12 chronic alcohol consumption,13 physical activity,14 obesity,15,16 and lipid-lowering
therapy have all been reported to influence LDL oxidation. Consequently, interregional variability in the degree of LDL oxidation might parallel the South-to-North gradient across Europe observed for the incidence and mortality of CAD. The aim of this study was to determine whether this LDL oxidation gradient exists in male subjects with stable CAD in three European regions by latitude.

Methods

Participants

The design of the study ‘Air Pollution and Inflammatory Response in Myocardial Infarction Survivors: Gene–Environment Interaction in a High Risk Group’ (AIRGENE) and its participant and clinical site recruitment and selection have been described previously. Briefly, this cross-sectional study conducted in stable male CAD participants in the AIRGENE Study grouped the six participating centres by order of latitude (South to North), i.e. Athens (Greece), Barcelona (Spain), Rome (Italy), Augsburg (Germany), Stockholm (Sweden), and Helsinki (Finland).

Definition of myocardial infarction (MI) was based on current international recommendations. Inclusion criteria were history of MI between 3 months and 6 years before inclusion and age between 35 and 79 years. Exclusion criteria were MI or revascularization procedures <3 months prior to the recruitment time, circumstances that precluded six consecutive monthly examinations, acute or chronic diseases, medical procedures or medication that would modify the biomarkers considered or prevent compliance with the study protocol. Currently non-smoking MI survivors were preferred for recruitment. Former smokers who had quit at least 3 months before the start of the study were considered non-smokers, although some centres (Athens, Barcelona, Rome) accepted light current smokers.

With our sample size, there was an 80% chance of reaching statistical significance for a difference of 6 U/L, \( P < 0.02 \), in oxLDL between two pairs of regions, assuming a standard deviation of 20 U/L.

All participants provided written informed consent and the local institutional Ethics Committees approved the protocol.

Questionnaires

Clinical measurements included blood pressure and body mass index (BMI), calculated as weight/height\(^2\) (kg/m\(^2\)).

The AIRGENE baseline questionnaire was based on the earlier panel study, Ultra II. It was administered to all participants by personal interview and physical activity, smoking history, environmental tobacco exposures, socio-economic status, and alcohol intake were assessed. History of CAD, other co-morbidity, and all medication taken were also recorded, including brand name, dose, and intake pattern. Acetylsalicylic acid, \( \beta \)-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs were taken into account for the purpose of our study.

Participants were considered non-smokers if they had not smoked for at least 3 months. Current alcohol intake was determined by asking participants how many glasses of wine, bottles of beer, and drinks or shots of brandy they consumed during the previous weekend and the most recent workday. From these data, a categorical alcohol consumption variable was created: abstainer, moderate consumer (\(<40\) g/L per day), and heavy consumer (\(\geq 40\) g/L per day). Physical activity during leisure time was assessed according to the type of activity and time devoted to physical activities. Participants were classified as inactive (\(<200\) kcal/week), partly active (200–900 kcal/week), or active (\(900\) kcal/week).

A brief food frequency questionnaire was administered to all participants to determine the monthly average number of servings of 12 food groups and the amount of fruit juice, red wine, and olive oil consumed during the preceding year. Vitamin supplement consumption was also requested. An antioxidant diet score was created to represent the antioxidant capacity of the participants’ diet. Frequency of consumption was coded from 1 (never or less than once per month) to 8 (four times or more per day) for the following food groups: olive oil, citrus fruits and berries, other fruits, green vegetables, and other vegetables. Red wine consumption was coded 4 for 1–2 glasses per day and 0 for non-consumers and all other consumption frequencies. Each group of foods was divided into quartiles and individual scores converted to a 1-to-4 score according to the individual quartile to which the participant belonged; the antioxidant score was the sum of these quartiles. The totals ranged from 5 to 24; the greater the score, the higher the likelihood that the participant followed a diet with antioxidant capacity.

Laboratory analyses

Venous blood was withdrawn according to a standard protocol into tubes containing EDTA-2Na (1 mg/mL) and was chilled on ice. Plasma was separated by centrifugation at 4 °C to measure oxLDL concentrations. Serum was separated within 60 min after withdrawal and kept frozen at –80 °C.

Total cholesterol and high-density lipoprotein (HDL) cholesterol were determined locally by standardized methods. LDL cholesterol and triglyceride levels were determined by a central laboratory using enzymatic methods (ABX Diagnostics, Montpellier, France) adapted to the Pentra-400 Autoanalyzer (ABX Diagnostics, Montpellier, France). Plasma concentration of oxLDL was performed in a central laboratory by a sandwich ELISA procedure using murine monoclonal antibody mAb-4E6 and a capture antibody bound to microtiter well plates and a peroxidase-conjugated antibody against oxidized apolipoprotein B bound to the solid phase (oxLDL, Mercodia AB, Uppsala, Sweden). Intra- and inter-assay coefficients of variation were 2.8 and 7.3%, respectively.

Fasting time before blood extraction varied among patients and centres. Postprandial oxidative stress occurs together within increase in triglyceride and glucose levels. Because of this, both conditions increase LDL susceptibility to oxidation. Consequently, oxLDL level was adjusted for triglyceride levels as a proxy for the time from last meal to blood withdrawal.

Statistical analyses

Normal distributions of continuous variables were assessed by normal probability plots. Triglyceride levels required log transformation to render a normal distribution. \( \chi^2 \), one-way ANOVA, and Kruskal-Wallis tests were used as appropriate to determine the relationship of potential confounders with the geographical area. OxLDL correlations with each participant characteristic were analysed by the Pearson, Spearman, and Student t-tests, as appropriate. A variable was considered a potential confounder when it was associated with oxLDL and with the country of origin at a significance level <0.15.

Three multivariable linear models adjusted for three different sets of variables were fitted to analyse whether oxLDL values followed a geographical pattern. The first model was adjusted for triglyceride level only. Potential confounders identified in univariate analyses were included in the second model. The third model added those variables known to influence LDL oxidation, regardless of whether they met statistical confounding criteria. Total cholesterol was not included in any model because of its high correlation with LDL cholesterol. Adjusted values of oxLDL were the fitted values at the mean of the adjustment variables for each region and model.

We tested the hypothesis that a gradient in oxLDL might exist across three geographical regions in Europe: Northern (N), Central (C), and Southern (S). Six possible sequences of increasing oxLDL values adjusted for co-variables exist: S–C–N, C–S–N, etc.
used a Bayesian approach to determine the probability of each sequence. To define this model in the Bayesian context, we assigned a prior distribution to all the coefficients as well as the residual variance. We considered any possible value of a given coefficient to have the same likelihood. After fitting the model to the data, the coefficients followed the Student t-distribution under these conditions. The posterior probabilities of the six possible sequences were computed from the posterior probability distribution of the three region coefficients $a_S < a_C < a_N$, $a_S < a_N < a_C$, etc. To compute the posterior region-sequence probabilities, a simulation of one million iterations was done. The error in every estimated probability (95% credible interval), which depends on the number of iterations performed, was <0.098%.

To elucidate whether an interaction existed between the geographical region and the LDL cholesterol levels or oxLDL, two additive linear models, including and excluding Italian participants, were computed.

Statistical analysis was done with R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria, Version 2.0).

Results

We included 790 male MI subjects, mean age 61.4 ± 9.5, out of the 1003 participants of the AIRGENE Study. Significant differences among countries were observed for age, physical activity, systolic blood pressure, diastolic blood pressure, BMI, antioxidant diet score, previous history of congestive heart failure, chronic bronchitis, emphysema and arthrosis, smoking, alcohol intake, lipid profile, oxLDL, and life-saving drug therapies (Tables 1 and 2). The Italian participants had the highest oxLDL levels. Table 3 shows participant characteristics by quartiles of oxLDL. Previous history of emphysema and arthrosis, alcohol intake, and lipid profile showed a significant relationship with oxLDL, which remained when Italian participants were excluded (data not shown).

The six participating countries were grouped in three regions by latitude: Northern (Finland and Sweden), Central (Germany), and South (Spain, Greece, and Italy). In Figure 1, we show the oxLDL levels in each region by LDL cholesterol tertiles with and without the Italian participants ($P$ for interaction = 0.444 and 0.549, respectively). In Northern and Central Europe, oxLDL was higher than in the South in all tertiles, but the difference was statistically significant in the lowest and the highest LDL cholesterol tertiles when we excluded Italian participants.

To fit the three adjusted models to analyse oxLDL by region, prior probability that geographical areas would follow an order in all three models was considered to be one-sixth (16.7%). Model 1 was adjusted for triglycerides only: oxLDL-adjusted values and 95% confidence intervals were 62.8 (60.5–65.0), 57.7 (54.4–61.0), and 62.3 (59.7–64.8) U/L for Southern, Central, and Northern Europe, respectively ($P$ = 0.037). The following potential confounders were included in the second model: geographical area, HDL and LDL cholesterol, previous history of emphysema and arthrosis, alcohol intake, age, and the antioxidant diet score. Total cholesterol was excluded from the analyses owing to the high correlation with cholesterol fractions, particularly LDL cholesterol. oxLDL-adjusted levels were 60.8 (58.6–63.0), 58.4 (55.3–61.4), and 64.8 (62.3–67.2) U/L for Southern, Central, and Northern areas, respectively ($P$ = 0.003) (Figure 2B). The sum of S–C–N and C–S–N probabilities (98.8%) yielded the probability for the Northern area to have a higher level of oxLDL than the other two

<table>
<thead>
<tr>
<th>Country</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece ($n = 94$)</td>
<td>Spain ($n = 141$)</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.001</td>
</tr>
<tr>
<td>Antioxidant diet score</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sedentary, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Emphysema, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arthrosis, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol intake ≥ 40 g/day, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE-inhibitors, n (%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lipid lowering, n (%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ACE, angiotensin-converting enzyme.

*Mean (standard deviation).
A third model (data not shown) was further adjusted for physical activity, BMI, and lipid-lowering treatment. The probability that the Northern area would have the highest level of oxLDL was 96.5% in this model.

A sensitivity analysis, excluding Italian participants, showed in the first model oxLDL-estimated values to be 58.0 (55.4–60.6), 57.6 (54.6–60.7), 62.1 (59.7–64.5) U/L ($P = 0.027$) for Southern, Central, and Northern areas, respectively.

(Figure 2B).
respectively. In the second model, oxLDL-adjusted levels were 56.5 (54.0–59.0), 57.6 (54.7–60.4), and 63.8 (61.5–66.1) U/L (Figure 2A). The probability that geographical areas would be ordered S–C–N was 71.4% (Figure 2B). In the third model, the probability of S–C–N was 74.5%.

Three models, adjusted for the same set of confounders as mentioned earlier, were fitted to test the country effect on oxLDL with and without Italian participants (Table 4). OxLDL coefficients in Italy, Finland, and Sweden were significantly higher than those observed in Spain (reference) in the fully adjusted models.

**Discussion**

In the present study, we observed that oxidative damage on LDL was lower in stable CAD patients from Southern European countries (Greece, Spain, and Italy) than in...
Central (Germany) and Northern Europe (Finland and Sweden). An increasing South-to-North gradient in LDL oxidation is most likely to exist, particularly when Italian participants were excluded of the analysis. This finding consistently held in all levels of LDL cholesterol: at any given amount of LDL cholesterol, the level of LDL oxidation was lower in Southern European countries.

Crude and adjusted oxLDL population values showed an interregional variability that paralleled the differences in mortality and incidence rates of CAD. Therefore, interregional variation in CAD incidence and mortality rates could in part be explained by different oxidative stress response capacity. The environmental or lifestyle factors that enhance metabolic mechanisms against oxidation could be less prevalent or weaker in Central and Northern regions.

In the present study, the lipid profile showed the most relevant association with LDL oxidation. These findings concur with previous findings in CAD patients. Therefore, higher blood total cholesterol and LDL cholesterol levels seem to result in an increased substrate for free radical action. However, our data show that, when we excluded Italian participants, populations of Southern Europe had higher total cholesterol and LDL cholesterol levels, together with lower oxLDL levels. At any level of LDL cholesterol, the oxLDL was lower in Southern and Central than in Northern Europe. These findings suggest that, particularly in Southern Europe, some factors other than those measured here may operate to prevent LDL from oxidation. OxLDL levels observed in Italian participants were by far the highest among the European countries tested. High triglyceride-to-HDL cholesterol molar ratio has been described as a proxy for small, dense LDL which increases the susceptibility to lipid peroxidative modification. The triglyceride-to-HDL cholesterol molar ratio was the highest of all in Italian participants, suggesting that their antioxidant capacity was limited.
Table 4

Sensitivity analysis of oxidized low-density lipoprotein-adjusted levels, including and excluding Italian participants

<table>
<thead>
<tr>
<th>Country</th>
<th>Including Italian participants</th>
<th>Excluding Italian participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1, ( n = 778 ), adjusted ( R^2 = 0.893 )</td>
<td>Model 2, ( n = 664 ), adjusted ( R^2 = 0.916 )</td>
</tr>
<tr>
<td></td>
<td>Model 1, ( n = 755 ), adjusted ( R^2 = 0.891 )</td>
<td>Model 2, ( n = 662 ), adjusted ( R^2 = 0.916 )</td>
</tr>
<tr>
<td>South</td>
<td>0.893, 95% CI (0.804 to 0.982)</td>
<td>0.916, 95% CI (0.825 to 1.007)</td>
</tr>
<tr>
<td>Centre</td>
<td>0.893, 95% CI (0.804 to 0.982)</td>
<td>0.916, 95% CI (0.825 to 1.007)</td>
</tr>
<tr>
<td>North</td>
<td>0.893, 95% CI (0.804 to 0.982)</td>
<td>0.916, 95% CI (0.825 to 1.007)</td>
</tr>
<tr>
<td>Spain</td>
<td>1.05, 95% CI (0.91 to 1.20)</td>
<td>1.15, 95% CI (0.98 to 1.32)</td>
</tr>
<tr>
<td>Greece</td>
<td>0.94, 95% CI (0.84 to 1.04)</td>
<td>1.04, 95% CI (0.93 to 1.15)</td>
</tr>
<tr>
<td>Italy</td>
<td>0.44, 95% CI (0.33 to 0.55)</td>
<td>0.59, 95% CI (0.47 to 0.72)</td>
</tr>
<tr>
<td>Germany</td>
<td>1.06, 95% CI (0.95 to 1.18)</td>
<td>1.20, 95% CI (1.08 to 1.32)</td>
</tr>
<tr>
<td>Finland</td>
<td>1.02, 95% CI (0.92 to 1.13)</td>
<td>1.17, 95% CI (1.06 to 1.29)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.52, 95% CI (1.36 to 1.69)</td>
<td>1.91, 95% CI (1.75 to 2.07)</td>
</tr>
</tbody>
</table>

Pairwise differences among North and Centre regions with South and among countries. Model 1: adjusted for triglycerides, high and low density lipoprotein cholesterol, age, alcohol.

The role of some lifestyle factors, such as some diet components, on lipid peroxidation has been found to be relevant to this phenomenon. A higher antioxidant diet score was related with lower LDL oxidation. Southern populations showed more antioxidant consumption, a characteristic of the Mediterranean diet pattern. The beneficial effect of this type of diet on the lipid profile has been reported, but heavy alcohol consumption seems to increase circulating oxLDL and to decrease the total anti-radical defence. We observed a greater number of heavy drinkers in the Central region, although they did not have the highest oxLDL level. It is important to point out the difficulty of distinguishing the effects of wine from those of total alcohol.

Stable male MI patients are known to have higher oxidative stress than healthy subjects. These higher baseline oxLDL levels could account for the apparent lack of influence of BMI on oxLDL levels in our study. Ageing has been reported to be associated with increased generation of oxidative stress and some antioxidant reduction in serum and blood lipids in the elderly. Similarly, physical activity increased significantly the whole blood resistance to free radicals. None of them were found to be related with oxLDL in our study. This may reflect the fact that all participants were stable male CAD subjects with relatively similar age and physical activity.

Despite the higher total and LDL cholesterol levels, oxLDL was lower in Southern Europe. This finding is consistent with the results reported by the Seven Countries study, in which a total cholesterol value of 5.2 mmol/L led to CAD mortality rates five times higher in Northern Europe than in Mediterranean Southern Europe. Total cholesterol and LDL cholesterol appear to not have the same meaning in all populations, possibly due in part to varying oxLDL.

Taken together, these findings support the hypothesis that environmental factors could play a key role in LDL oxidation differences between patients when clinical status is similar. Countries in Northern Europe seem to have a worse defence against oxidation. Oxidative theory of atherosclerosis indicates that elevated levels of circulating oxLDL result in plaque instability and more severe acute coronary events and have been considered a biochemical marker for CAD.

The study design was ecological in nature as far as the hypothesis is sustained by population CAD incidence and mortality rates. However, the individual data allowed us to distinguish the lifestyle effect from those stemming from interregional variability alone. The fact that only male CAD patients were included to test the hypothesis of oxLDL association with CAD incidence and mortality rates limits the external validity of the study. On the other hand, the high prevalence of lung diseases among Italian participants could make them unrepresentative of the population of CAD at large. Further studies on healthy male and female representatives of a greater variety of European countries and the results of international combined cohort studies in Europe should contribute to a more complete assessment of our hypothesis.

In conclusion, an increasing S–C–N gradient of oxLDL levels, a biomarker of lipid peroxidation, is observed across Europe in men with stable CAD and holds true at all levels of LDL, except for Italy; this country has the highest levels in Europe, for unknown reasons.
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Conflict of interest: none declared.

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References


Clinical vignette

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A dangerous arrow

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A 75-year-old man underwent yearly follow-up carotid Duplex scanning after carotid endarterectomy (CEA), performed 3 years ago, because of the presence of a large atherosclerotic plaque at the bifurcation of left common carotid artery with severe stenosis (80%). A residual atheroma was present post-CEA with a small stenosis.

His medical history was notable for well-controlled hypertension, type 2 diabetes mellitus, smoking, and hypercholesterolemia; his medications were simvastatin, aspirin, enalapril, and metformin. He was asymptomatic and there was a left carotid bruit on examination.

Longitudinal carotid ultrasonography (Panel A) and power-Doppler imaging (Panel B) showed an ulcerated plaque below the left CEA, strongly resembling an arrow, with severe stenosis of 90% confirmed by conventional angiography (Panel C; the arrow indicates the severe stenosis and the arrowhead indicates the CEA).

Percutaneous transluminal angioplasty with stenting and cerebral protection using filter devices was successfully performed (Panels D and E, arrows).

No neurological deficits or cranial nerve palsy were noted after the procedure, and at 6 months of follow-up, the patient was asymptomatic, without signs of restenosis (Panel F).

Panel A. Longitudinal carotid ultrasonography showing the residual ulcerated plaque with severe 90% stenosis, below the left CEA, strongly resembling an arrow.

Panel B. Longitudinal carotid power-Doppler imaging showing the narrowed left common carotid artery, strongly resembling an arrow.

Panel C. Conventional digital subtraction angiography showing the severe stenosis (arrow) below the left CEA (arrowhead).

Panel D. Conventional digital subtraction angiography showing the stent (arrow) with normal blood flow after percutaneous transluminal angioplasty.

Panel E. Conventional Angiography showing the stent (arrow) after percutaneous transluminal angioplasty.

Panel F. Longitudinal carotid power-Doppler imaging showing the stent with normal blood flow.