Lipoprotein (a) and coronary heart disease among women: beyond a cholesterol carrier?

Iris Shai1,2,7*, Eric B. Rimm1,2,3, Susan E. Hankinson2,3, Carolyn Cannuscio4, Gary Curhan3, JoAnn E. Manson2,3,5, Nader Rifai6, Meir J. Stampfer1,2,3, and Jing Ma2,3

1 Department of Nutrition, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; 2 Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; 3 Channing Laboratory, Department of Medicine, Brigham Women Hospital and Harvard Medical School, Boston, MA, USA; 4 Merck Research Laboratories, Merck & Co. Inc., Whitehouse Station, NJ, USA; 5 Division of Preventive Medicine, Department of Medicine, Brigham Women Hospital and Harvard Medical School, Boston, MA, USA; 6 Department of Laboratory Medicine, Children’s Hospital and Harvard Medical School, Boston, MA, USA; and 7 Department of Epidemiology, S. Daniel Abraham International Center for Health and Nutrition, Ben-Gurion University, Beer-Sheva, Israel

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Aims With its homology with plasminogen, lipoprotein(a) [Lp(a)] may be related to thrombosis and inflammation. We assessed the role of Lp(a) in coronary heart diseases (CHD) by a recently developed assay that is not affected by the plasminogen-like Kringle-type-2 repeats.

Methods and results Of 32 826 women from the Nurses’ Health Study, who provided blood at baseline, we documented 228 CHD events during 8 years of follow-up. Each case was compared with two matched controls. In a multivariable model adjusted for body mass index, family history, hypertension, diabetes, post-menopausal hormone use, physical activity, blood drawing characteristics, and alcohol intake, the odd ratio (OR) for Lp(a) levels > C 30 mg/dL was 1.9 (95% CI: 1.3–3.0) when compared with those with Lp(a) <30 mg/dL. Women with high levels of both Lp(a) (>30 mg/dL) and fibrinogen (>400 mg/dL) had an OR of 3.2 (95% CI: 1.6–6.5) for CHD, when compared with the combination of low levels (P interaction = 0.05). Women with high levels of both Lp(a) and C-reactive protein (>3 mg/L) had an OR of 3.7 (95% CI: 2.03–6.64) for CHD, when compared with the combination of low levels (P interaction = 0.06).

Conclusion Lp(a) levels >30 mg/dL are associated with twice the risk of CHD events among women and may be related to thrombosis and inflammation.

KEYWORDS CHD; Lipoprotein(a); Apolipoprotein(a); Fibrinogen; C-reactive protein

Introduction Lipoprotein (a) [Lp(a)], is an LDL-like particle in which an apolipoprotein(a) [apo(a)] moiety is linked via a disulfide bond to apolipoprotein B100 (apoB100). In a meta-analysis, Lp(a) has been identified as a modest risk factor for coronary events, with a summery risk ratio of 1.6 (95% CI: 1.4–1.8) in the top vs. bottom tertiles. Although a similar association for both genders is suggested, data for women are sparse and inconsistent.

In addition to its role as a cholesterol carrier, Lp(a) may be involved in both inflammation and thrombosis. Lp(a) was significantly associated with acute phase proteins and was found to promote proliferation of vascular smooth muscle cells and chemotaxis of human monocytes. Its role in atherothrombosis is suggested by the structure of apo(a). This large multikringle glycoprotein shares 89% sequence homology with plasminogen, the main activator of the fibrinolytic system. Thus, Lp(a) may compete for the plasminogen receptor and reduce fibrinolysis.

Apo(a) varies in size from 300 to 800 kDa, depending on the number of plasminogen-like Kringle IV-type-2 repeats. This size polymorphism is an important determinant of the density heterogeneity of Lp(a), and is one of the significant sources of discrepancy among Lp(a) assays in the past. In this study, we measured Lp(a) with an assay that is not affected by the Kringle IV-type-2 repeats, a method that became available only recently.

In the Nurses’ Health Study (NHS) cohort of middle-aged women, we assessed the predictive value of Lp(a) in relation to coronary heart disease (CHD) compared with the traditional lipid biomarkers and biomarkers of inflammation and thrombosis.

Methods

The NHS cohort population and blood collection

The NHS was initiated in 1976, with the enrollment of 121 700 female nurses aged 30–55. Since then, follow-up questionnaires
have been mailed to the cohort every 2 years to update information on exposures and the occurrence of major illnesses. Between 1989 and 1990, blood samples were collected from 32,826 women. Of the samples, 97% were returned within 24 h of collection. They were immediately centrifuged, aliquoted into plasma, red blood cell, and buffy-coat fractions, and stored in vapour-phase liquid nitrogen. The study was approved by the institutional review boards at the Harvard School of Public Health and the Brigham and Women’s Hospital; completion of the self-administered questionnaire was considered to imply informed consent.

Assessment of CHD end points

The endpoint for this study comprised incident cases of non-fatal myocardial infarction (MI) and fatal CHD that occurred after the blood collection and before 31 May 1998. Subjects with a previous report of cancer or CHD before the blood collection were excluded. Cases were confirmed if they met the diagnostic criteria of the World Health Organization (i.e. symptoms plus either cardiac enzyme level elevations or diagnostic ECG changes).15 Physicians reviewed medical records blinded to exposure status. MI was defined as probable if medical records were not available but hospitalization occurred, and confirmatory information was obtained by interview or letter. Systematic searches of the state vital records and the National Death Index identified >98% of deaths.16 Fatal CHD was defined as fatal MI confirmed by hospital records or at autopsy or as CHD recorded on the death certificate, if this was the underlying and most probable cause given and there was previous evidence of CHD. In no instance was the cause on the death certificate accepted without corroboratation. Total CHD was defined as non-fatal MI plus fatal CHD. Each case was matched, with replacement, by year of age (to ±1 year), year and month of blood draw (same year, ±2 month), fasting status before blood draw (lower/higher than 8 h), and smoking status (never, past, current) to two controls who were free of CHD at the time of the case diagnosis.

Laboratory methods

Lipid biomarkers, C-reactive protein and fibrinogen assays were performed in the laboratory of Dr Nader Rifai (The Children’s Hospital, Boston, MA, USA), which is certified by the NHLBI/CDC Lipid Standardization program. All the methods except the enzyme-linked immunosorbent assay and radioimmuno assay were done on the Hitachi 911 analyser (Roche Diagnostics, Indianapolis, IN, USA). Lp(a) was measured by a latex-enhanced immunoturbidimetric method (Denka Sieken, Tokyo, Japan) with a coefficient of variation (CV) of 2.6%. This method is the only commercial assay that is not affected by the Kringle IV-type-2 repeats.14 Total cholesterol was measured enzymatically with CV <1.7%. Concentrations of triglycerides (TGs)18 and HDL-cholesterol (HDL-c) were analysed simultaneously on the Hitachi 911, with CVs of 1.75 and 2.5%, respectively. LDL-c was measured by a homogenous direct method (Genzyme, Cambridge, MA, USA), with a CV <3.1%. Total apoB100 and C-reactive protein were measured by an immunoturbidimetric technique on the Hitachi 911 analyser, with CVs of 4.33 and 1.4%, respectively. Fibrinogen was measured by an immunoturbidimetric assay on the Hitachi 911 analyser with reagents and calibrators from Kamiya Biomedical Co. (Seattle, WA, USA) for testing an antigen-antibody reaction and agglutination, with a CV of 1.16%. Homocysteine (Hcy) was determined by an HPLC method,17 with a CV of 2.9%

Data analysis

We compared the characteristics of the case–control groups by Student’s t-test for the continuous variables, χ² test for categorical variables, and non-parametric Wilcoxon test for Lp(a) and TGs, which were right-skewed. Quintile cut-points were defined according to the control levels of Lp(a). We used general linear models to determine the adjusted mean level of plasma biomarkers across quintiles of Lp(a), controlled for age, smoking, body mass index (BMI), characteristics of blood at return, and outcome status (case/control). P-value for trend across the quintiles was assessed by the weighted regression of the median quintile points. After classifying the study populations into quintiles based on the distribution of control values, we used conditional logistic regression analyses to compute odd ratios (ORs) of future CHD with 95% confidence intervals (CI). In addition to the matching criteria, we included in our multivariable models the following traditional CHD risk factors: BMI (<25, 25 to ≤30, >30 kg/m²), parental history of MI (before 60 years), hypertension, diabetes, post-menopausal hormone use, physical activity (METs/week, quintiles), blood drawing characteristics (no problems, >1 day since drawn, moderate haemolysis), and alcohol intake (quintiles). We further added to the multivariable model, each one at a time, the following biomarkers to look for confounders: LDL-c, HDL-c, TGs, apoB100, tC/HDL, C-reactive protein, and fibrinogen.

In unconditional logistic regression analysis, we used a likelihood ratio test (LRT) to determine whether the addition of Lp(a) screening to traditional risk factors, standard lipids profile, and apoB100 significantly improved risk prediction models. We estimated the joint effect between Lp(a) and selected biomarkers in multivariable unconditional logistic regression analysis. We classified the entire study population into one of four groups. The cut point for Lp(a) was ≥30 mg/dL.18,19 The cut point for high fibrinogen was ≥400 mg/dL, which was used previously,15 and represented the approximate top quintile, cut-point (418.5 mg/dL) among the control group. The cut points of high C-reactive protein (≥3 mg/L), high LDL-c (≥160 mg/dL),21 and low HDL-c (≤40 mg/dL)21 were chosen by standard definitions. An interaction term was created for each analysis by multiplying the combinations of each group. Its significance has been tested in a multivariable model, including the individual component of each group. All the analyses were two sided. We analysed the Lp(a) variable by categories rather than its continues form because Lp(a) is normally distributed, and as the association with CHD appears to be non-linear, with a suggested of threshold effect at the highest quintile. In Figure 1 as we computed relative risks across groups with combined characteristics, we could not compare the specific matched triplets and have used unconditional logistic regression, as well as in Table 2, when assessing correlations. However, in both analyses we adjusted for the matched factors, as indicated.

Results

Population characteristics and biomarker means across quintiles of Lp(a)

After excluding 24 women who were taking cholesterol-lowering drugs at blood draw and 50 women with missing Lp(a) levels, we analysed 228 incident cases of CHD (193 non-fatal MI, 35 fatal CHD) and 445 matched controls. The cases had higher BMI and were more likely to have diabetes, hypertension, and a parental history of MI than were the controls. Lp(a) and the other lipid biomarkers were significantly higher among the cases (Table 1). Table 2 shows multivariable-adjusted mean levels of plasma biomarkers across quintiles of Lp(a). Lp(a) was positively associated with apoB100, LDL-c, and total cholesterol levels. In contrast, levels of TGs were lower across higher quintiles of Lp(a). Levels of fibrinogen, C-reactive protein, and Hcy were not associated with Lp(a) concentrations. Lp(a) levels did not vary across BMI groups or by smoking or hormone-replacement therapy status (data not shown). We found similar patterns when analysing data only from the control group.
Figure 1  Relative risks computed across groups with combined characteristics.
Prediction models

The OR of Lp(a) for CHD was 1.85 (95% CI: 1.09–3.13) for the highest vs. the lowest quintile in a matched model and 2.09 (95% CI: 1.16–3.77) in a multivariable model (Table 3). As our results suggested a non-linear association between Lp(a) and risk of CHD, we estimated the OR (Table 4) for patients with concentrations above and below 30 mg/dL, a suggested cut-point\(^{18,19}\) that closely represents the 80th percentile of the control distribution of Lp(a) (the 81th percentile). We further controlled for lipid and non-lipid biomarkers to look for confounders. The OR of CHD associated with Lp(a) levels \(\geq 30\) mg/dL was 1.77 (1.20–2.60) in the matched model, and 1.95 (95% CI: 1.27–3.00) in the multivariable model. The magnitude of this association did not appreciably change after further adjustments for LDL-c, HDL-c, TGs, apoB 100, tC/HDL, C-reactive protein, or fibrinogen.

The residual contribution of Lp(a) to the prediction of CHD in a multivariable model

As expected, the following group of CHD risk factors: C-reactive protein and Hcy levels, age, smoking status, BMI, parental history, hypertension, diabetes, physical activity, and alcohol intake, significantly (\(P\) LRT, \(0.0001\)) predicted future risk of CHD. Addition of LDL-c, HDL-c, TGs, and apoB\(_{100}\) to the multivariable model significantly improved the prediction of CHD (\(P\) LRT < 0.0001). Finally, addition of the individual variable Lp(a) to the multivariable model described earlier independently increased information beyond that provided by the traditional lipid biomarkers and apoB\(_{100}\), (\(P\) LRT = 0.006).

Joint effect of Lp(a) with selected CHD risk factors

We explored the joint effect between Lp(a) and selected CHD risk factors related to the suggested roles of Lp(a).\(^{7,10}\) In a multivariable model (Figure 1A), we found a suggestion of an interaction between Lp(a) and fibrinogen. Among women in the high levels of both Lp(a) and fibrinogen, the OR of CHD was 3.21 (95% CI: 1.57–6.53), compared with women in the lower levels both biomarkers (\(P\) interaction = 0.05). Further adjustment for C-reactive protein did not change the associations (data not shown). In the multivariable model (Figure 1B), only the combination of high levels of both Lp(a) and C-reactive protein was significantly associated with CHD [OR = 3.67 (95% CI: 2.03–6.64), \(P\) interaction = 0.06]. The combination of high Lp(a) and LDL-c levels (Figure 1C) produced an additive effect [OR = 3.82 (95% CI: 1.85–7.87)], with no suggested interaction. Similarly, high Lp(a) levels combined with low HDL-c levels produced an additive effect [OR = 4.06 (95% CI: 1.24–13.32)], with no suggestion of interaction.

Discussion

The current results suggest that Lp(a) levels \(\geq 30\) mg/dL are associated with twice the risk of first CHD event among women. Measurement of Lp(a) by this recently validated method\(^{14}\) demonstrates that Lp(a) provides predictive information beyond that provided by established lipid and non-lipid risk factors. The robust association of Lp(a) with CHD, independent of lipid risk factors could be driven by its potential role in inflammation and thrombosis.

Our study has several limitations. First, single measurements of biomarkers may be insufficient to explore individual variation over time. Thus, the effects we have observed may be underestimated owing to random measurement error. However, variation in plasma Lp(a) levels is determined mostly by inheritance at the apo(a) gene locus.\(^{22}\) Secondly, although we found most of our biomarkers to be stable if blood specimens were processed within 36 h of collection,\(^{23}\) Lp(a) and fibrinogen appeared to be stable only up to 24 h. However, 97% of the samples were returned within 24 h of collection and controlling for matching factors and laboratory parameters should have reduced this error. Thirdly, measurement of Lp(a) in frozen samples is likely to result in a preferential decrease and false lower Lp(a) concentrations in samples with low-molecular-weight apo(a) isoforms in CHD cases compared with control groups.\(^{24}\) This degradation, if presented, may
Table 1  Baseline characteristic of the NHS population

<table>
<thead>
<tr>
<th>Variable</th>
<th>228 cases of CHD</th>
<th>445 controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>61.5 ± 6.5</td>
<td>61.0 ± 6.7</td>
<td>Matching factor</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>34.4</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>34.5</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>31.1</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 ± 6.1</td>
<td>25.3 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental MI before age 60 (%)</td>
<td>21.8</td>
<td>12.7</td>
<td>0.01</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>37.6</td>
<td>18.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>13.3</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Menopausal status (%)</td>
<td>90.2</td>
<td>87.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Post-menopausal hormone use (%)</td>
<td>29.9</td>
<td>36.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Lp(a)b (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile)</td>
<td>10.8 (5.2–40.2)</td>
<td>8.7 (4.3–21.7)</td>
<td></td>
</tr>
<tr>
<td>ApoB100 (mg/dL)</td>
<td>129.8 ± 36.4</td>
<td>114.4 ± 31.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>52.0 ± 14.3</td>
<td>60.3 ± 17.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>144.6 ± 34.2</td>
<td>132.9 ± 36.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceridesb (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile)</td>
<td>128 (91–196)</td>
<td>108 (73–148)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>231.4 ± 40.4</td>
<td>225.2 ± 39.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*±SD for mean values.

aAdjusted for age, smoking (never, past, current), BMI (≤25, >25 to ≤30, >30 kg/m²), blood drawing characteristics (no problems, >1 day since drawn, moderate haemolysis), and case-control status.

Table 2  Multivariablea-adjusted mean levels (±SE) of plasma biomarkers across quintiles of Lp (a)

<table>
<thead>
<tr>
<th>Lp(a) quintilesb</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
</tr>
<tr>
<td>Median (mg/dL)</td>
<td>2.1</td>
</tr>
<tr>
<td>Range</td>
<td>0.1–3.4</td>
</tr>
<tr>
<td>Plasma biomarkers</td>
<td></td>
</tr>
<tr>
<td>ApoB100 (mg/dL)</td>
<td>114.4 (2.8)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>129.7 (3.1)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>57.6 (1.4)</td>
</tr>
<tr>
<td>Triglyceridesb (mg/dL)</td>
<td>133.0 (1.1)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>225.9 (3.5)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>350.8 (8.0)</td>
</tr>
<tr>
<td>CRPc (mg/L)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>Hcyc (µmol/mL)</td>
<td>10.6 (1.0)</td>
</tr>
</tbody>
</table>

aAdjusted for age, smoking (never, past, current), BMI (≤25, >25 to ≤30, >30 kg/m²), blood drawing characteristics (no problems, >1 day since drawn, moderate haemolysis), and case-control status.
bQuintiles were defined according to the control blood level distribution.

cGeometric mean.

Table 3  OR (95% CI) of CHD across quintiles of Lp(a)

<table>
<thead>
<tr>
<th>Lp(a) quintiles</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched</td>
<td>1 (ref.)</td>
<td>1.10 (0.63–1.93)</td>
<td>1.09 (0.62–1.92)</td>
<td>0.98 (0.55–1.74)</td>
<td>1.85 (1.09–3.13)</td>
</tr>
<tr>
<td>Multivariablea</td>
<td>1 (ref.)</td>
<td>1.18 (0.63–2.20)</td>
<td>1.05 (0.55–1.98)</td>
<td>1.09 (0.58–2.03)</td>
<td>2.09 (1.16–3.77)</td>
</tr>
</tbody>
</table>

aMultivariable conditional regression (matched for age and smoking), adjusted for BMI (≤25, >25 to ≤30, >30 kg/m²), parental history (parental MI before 60 years), hypertension, diabetes, post-menopausal hormone use, physical activity (METs/week, quintiles), blood drawing characteristics (no problems, >1 day since drawn, moderate haemolysis), and alcohol intake (quintiles).
dicting CHD events, beyond that provided by traditional
cohort, Lp(a) could contribute further information in pre-
was found in a larger women cohort. 6 In our women
in Lp(a) levels that parallels the age-related increase in
men, whereas women show a distinct age-related increase
action, rather than an additive effect.
low HDL-c, hypertension, 26 or hyperhomocysteinaemia.
crease the coronary risk with the presence of high LDL-c,
ated with life style factors or non-lipid biomarkers. In pro-
ments we used for Lp(a)14 and the direct measurement of
confounding by those factors. The independent measure-
factors had a minimal influence on the association of Lp(a)
by methodologic biases. As controlling for established risk
study reduce the possibility that our findings are affected
levels.25 We did not have information on impaired renal func-
levels.22 Indeed, Lp(a) levels were not associ-
rapta and this could account for their increased Lp(a)
levels.22 We did not have information on impaired renal func-
charges for diabetes and hypertension may
not sufficiently correct for impaired renal function. Finally,
the NHS does not represent a random sample of US women.
However, the socio-educational homogeneity of the cohort
may reduce other unknown confounders, and the clinical
implication may apply to populations with Lp(a) levels
>30 mg/dL.

The prospective design and high follow-up rates in this
study reduce the possibility that our findings are affected
by methodologic biases. As controlling for established risk
factors had a minimal influence on the association of Lp(a)
with CHD, our results are unlikely to be explained by residual
confounding by those factors. The independent measure-
ment we used for Lp(a)14 and the direct measurement of
LDL-c may strengthen the validity of our results.

Apo(a) gene accounts for >90% of the variation in plasma
Lp(a) concentrations.22 Indeed, Lp(a) levels were not associated
with life style factors or non-lipid biomarkers. In prospec-
tive studies, elevated Lp(a) levels were found to
increase the coronary risk with the presence of high LDL-c,
low HDL-c, hypertension,26 or hyperhomocysteinaemia.
Lp(a), as LDL-c, delivers a rich source of cholesterol to
sites of vascular injury. Previous prospective studies have
suggested that the effect of Lp(a) levels may depend on
the levels of other lipids and to interact positively with
adjusted plasma total/HDL-c ratio.27 We tested the joint
effect of Lp(a) with LDL-c and HDL-c and found no inter-
action, rather than an additive effect.

Levels of Lp(a) tend to remain constant with age among
men, whereas women show a distinct age-related increase
in Lp(a) levels that parallels the age-related increase in
LDL cholesterol.28 Lp(a) has been modestly associated
with CHD in two large prospective studies,4, 5 but no association
was found in a larger women cohort.4 In our women
cohort, Lp(a) could contribute further information in pre-
dicting CHD events, beyond that provided by traditional
CHD factors, lipid biomarkers, and apoB_{100}, suggesting
that Lp(a) may have different roles than other lipids in
atherosclerosis.

Whereas fibrinogen levels were not correlated with Lp(a),
we observed a suggestion of joint effect between Lp(a) and
fibrinogen in the background of multivariable risk factors.
Our results confirms a suggestion of joint effect of both bio-
markers among men in a study, where Lp(a) was not associ-
ated with CHD and no significant interaction was found.11
Fibrinogen, as a circulating glycoprotein, acts at the final
step in the coagulation response to vascular and tissue
injury.29 Apo(a) has been shown to attenuate fibrin clot
ysis both in vitro30 and in vivo,31 and its role in inhibition
of fibrinolysis has been suggested among men.11 Aside
from its role in thrombosis, fibrinogen is an acute-phase
reactant.32 Lp(a) is suggested to induces monocyte chemot-
astic activity in human vascular endothelial cells.8 Thus,
it is possible that the suggestion of interaction we observed
may point to the association of Lp(a) with inflammation.

Our results suggest that Lp(a) levels >30 mg/dL are
associated with twice the risk of CHD events among
middle-age women, independent from lipid, and non-lipid
CHD risk factors. Most of the cholesterol-lowering drugs,
with the exception of niacin-containing agents,33 are tar-
ged to LDL-c and are less effective against Lp(a).34

Assessing the residual risk of CHD in association with Lp(a)
could provide further understanding to the different roles
of LDL-c and Lp(a) in CHD.

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of conflict of interest.

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**Table 4** Multivariable OR (95% CI) of CHD associated with Lp(a)
levels >30 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Odd ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched</td>
<td>1.77 (1.20–2.60)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV</td>
<td>1.95 (1.27–3.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ LDL-c</td>
<td>1.96 (1.26–3.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ HDL-c</td>
<td>2.10 (1.35–3.26)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ TGs</td>
<td>2.11 (1.36–3.28)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ apoB100</td>
<td>1.94 (1.24–3.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ TC/HDL-c ratio</td>
<td>2.11 (1.34–3.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ CRP</td>
<td>1.95 (1.27–3.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV+ fibrinogen</td>
<td>1.96 (1.27–3.01)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*MV, multivariable conditional regression (matched for age and
smoking), adjusted for BMI (<25, >25 to <30, >30 kg/m²), parental
history of MI (before 60 years), hypertension, diabetes, post-
menopausal hormone use, physical activity (METS/week, quintiles),
blood drawing characteristics (no problems, >1 day since drawn, moder-
ate haemolysis), and alcohol intake (quintiles).

*The adjusted biomarkers were in quintile groups.


