

# Which Are the Determinants of Dyslipidemia in Rheumatoid Arthritis and Does Socioeconomic Status Matter in This Context?



Atherosclerotic cardiovascular disease (CVD) is the leading cause of death worldwide<sup>1</sup>. Although many genetic and environmental factors contribute to CVD, lipoproteins remain the pivotal agents in atherosclerosis<sup>1</sup>. Patients with rheumatoid arthritis (RA) experience a 2- to 3-fold increased risk for atherosclerotic CVD, a phenomenon that is likely attributable to unfavorable effects of cytokine-mediated high-grade inflammation on traditional risk factors such as insulin sensitivity and its direct adverse effects on the vasculature<sup>2</sup>. The ameliorations in traditional CV risk factor profiles<sup>3-5</sup> and interleukin 6-related endothelial dysfunction<sup>6</sup> upon disease activity suppression in RA support this paradigm.

Considering the fundamental role of dyslipidemia in atherosclerosis in non-RA subjects prompts the question whether RA characteristics alter lipoprotein profiles. Such potential interactions have been the topic of numerous studies performed over the past 3 to 4 decades. As applies to other inflammatory conditions<sup>7</sup>, high-grade inflammation or disease activity in the context of RA results in a reduction in total and low-density lipoprotein (LDL) cholesterol and a more consistent and marked decrease in high-density lipoprotein (HDL) cholesterol, thereby increasing the atherogenic index, i.e., the total cholesterol/HDL cholesterol ratio<sup>3,4</sup>. Treatment with traditional disease modifying agents for rheumatic disease (DMARD) and glucocorticoids reverses these changes<sup>3,4</sup>, an effect that may be less consistent with tumor necrosis factor- $\alpha$  blockade<sup>8</sup>. The increase in total and LDL cholesterol with traditional DMARD therapy can be prevented by insulin sensitivity-enhancing dietary intervention<sup>3</sup>.

Currently recommended treatment strategies generally comprise aggressive use of DMARD as soon as the disease is diagnosed. As a consequence, the typical RA patients may now no longer experience high-grade inflammation-induced dyslipidemia except during the time prior to seeking medical

care. In this new era, then, do lipoprotein profiles differ in established treated RA as compared to in non-RA subjects? This question is addressed by Garcia-Gómez and colleagues in this issue of *The Journal*<sup>9</sup>. The authors report on a range of lipid variables. Proatherogenic cholesterol is present not only in LDL but also in very low-density and intermediate-density lipoproteins, whereas cholesterol in HDL is antiatherogenic<sup>2</sup>. Accordingly, although LDL cholesterol concentrations currently constitute the primary target of therapy in guidelines for the management of CVD risk, recent evidence suggests that non-HDL cholesterol (total cholesterol minus HDL cholesterol) may be more appropriate in this context<sup>1</sup>. With regard to CVD risk prediction, ratios that include both a proatherogenic and an antiatherogenic lipid measurement, particularly the atherogenic index and the apolipoprotein B/A-1 ratio, outperform other lipid variables<sup>1,10</sup>. Garcia-Gómez and colleagues found that, as compared to control subjects from a population-based study, women with RA had lower atherogenic indices and both women and men with RA had lower apolipoprotein B/A-1 ratios. These differences were mainly driven by higher antiatherogenic HDL cholesterol and lower proatherogenic apolipoprotein B concentrations, respectively, in patients with RA. Lipoprotein(a) concentrations were increased in RA, but the independent role of this lipid variable in atherogenesis is controversial<sup>11</sup>. Taken together, the findings by Garcia-Gómez and colleagues indicate that classical lipoprotein-induced atherogenicity may be decreased in patients with established treated RA. The authors performed a multivariable analysis revealing that glucocorticoids may explain the higher HDL concentrations as experienced by patients with RA. Yet chronic glucocorticoid exposure is associated with enhanced atherosclerosis<sup>12</sup> and overall risk of myocardial infarction in RA<sup>13</sup>. The authors did not report whether the lower atherogenic index and apolipoprotein B/A-1 ratios in RA patients were explained by RA charac-

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See Conventional lipid profile and lipoprotein(a) concentrations in treated patients with RA, *page 1365*

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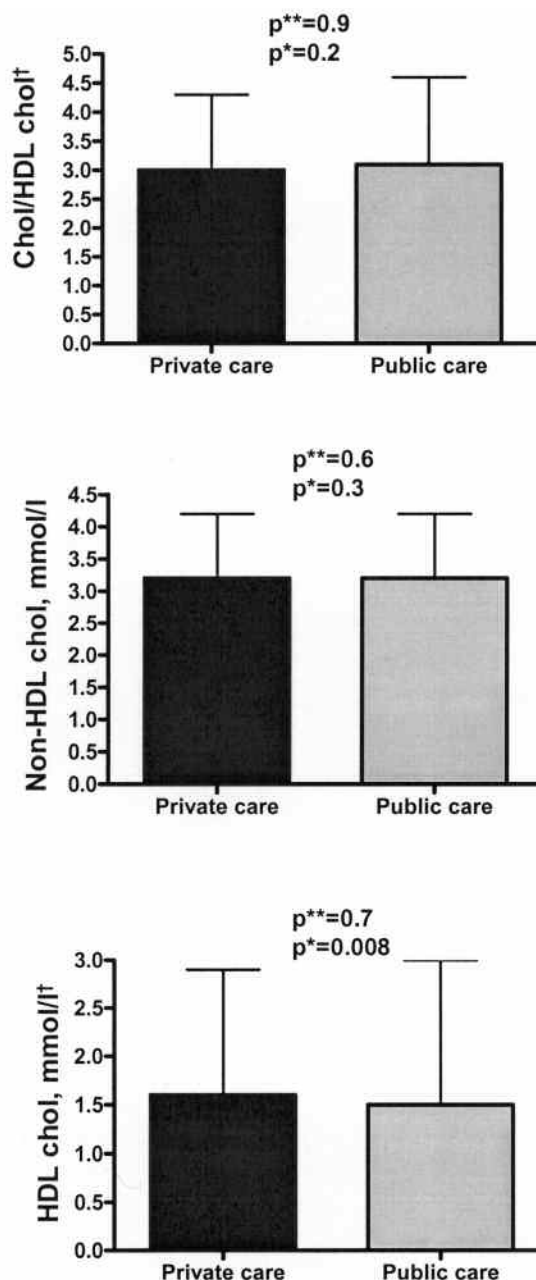
**Table 1.** Potential risk factors for dyslipidemia in 202 private care and 424 public care patients with rheumatoid arthritis. Data were compared between private and public care patients by the chi-square test (dichotomous variables) and Student t test (continuous variables). Characteristics that differed ( $p < 0.05$ ) between the 2 groups are shown in bold type.

Risk Factor	Private Care	Public Care
<b>Demographics</b>		
Age, yrs, mean (SD)	56.2 (12.1)	55.7 (11.4)
<b>Women, %</b>	<b>80.2</b>	<b>86.6</b>
<b>European, %</b>	<b>83.2</b>	<b>14.4</b>
<b>Black, %</b>	<b>4.5</b>	<b>66.5</b>
Asian, %	8.4	11.1
Mixed, %	4.5	8.0
<b>Lifestyle</b>		
<b>Smoking, %</b>	<b>15.3</b>	<b>9.5</b>
<b>Alcohol, %</b>	<b>42.1</b>	<b>1.7</b>
Exercise, %	13	NR
<b>Waist girth, cm, mean (SD)*</b>	<b>87 (1)</b>	<b>91 (1)</b>
<b>RA disease activity</b>		
<b>DAS28, mean (SD)</b>	<b>2.4 (1.4)</b>	<b>3.2 (1.5)</b>
<b>DMARD, mean (SD)</b>		
<b>Methotrexate, %</b>	<b>72.3</b>	<b>92.3</b>
<b>Chloroquine, %</b>	<b>54.5</b>	<b>88.2</b>
<b>Leflunomide, %</b>	<b>34.2</b>	<b>16.1</b>
Minocycline, %	17.8	12.4
Sulfasalazine, %	10.4	13.3
<b>Azathioprine, %</b>	<b>6.9</b>	<b>17.8</b>
Penicillamine, %	2.5	1.9
<b>Cyclophosphamide, %</b>	<b>0.5</b>	<b>6.7</b>
TNF- $\alpha$ blockade, %	3.0	0.0
<b>No. DMARD, mean (SD)</b>	<b>2.0 (0.9)</b>	<b>2.5 (0)</b>
<b>Any DMARD, %</b>	<b>94.1</b>	<b>99.5</b>
Prednisone, %	6.9	3.4
Statin, %	5.2	6.5

\* Geometric means and SD are given since this characteristic was non-normally distributed. NR: not recorded; DAS28: Disease Activity Score in 28 joints; TNF: tumor necrosis factor.

teristics. The findings by Garcia-Gómez and colleagues need to be replicated, and their implications in the reported excess CVD risk in RA and in the CVD risk assessment of the individual patient with RA require further investigation.

In the population at large, proatherogenic and antiatherogenic lipoprotein concentrations and their ratios are substantially determined not only by demographic features but also by lifestyle factors and excess adiposity<sup>14</sup>. Further, socioeconomic disadvantage adversely affects CV event rates both through unfavorable effects on traditional CVD risk factors and through psychosocial stress<sup>15</sup>. If these factors interact similarly with lipoprotein concentrations in RA, then they should be considered in future studies on lipoprotein-mediated CVD risk in this disease. This would allow for more adequately explaining the differences in lipoprotein profiles between subjects with and without RA. Further, quantification of the relative contribution of these potential determinants as compared to RA characteristics to dyslipidemia should help in the management of CVD risk in the individual patient with RA.



**Figure 1.** Total cholesterol/HDL cholesterol ratio (atherogenic index), non-HDL cholesterol, and HDL cholesterol in private and public care patients. Results are expressed as mean (SD) (non-HDL cholesterol) or geometric mean (SD) when the variables were non-normally distributed (total cholesterol/HDL cholesterol ratio and HDL cholesterol). Chol/HDL chol: total cholesterol/HDL cholesterol ratio; non-HDL chol: non-HDL cholesterol; HDL chol: HDL cholesterol. \*Univariate analysis (Student t test). \*\*Multivariable regression models in which age, gender, waist girth, smoking and alcohol status, the Disease Activity Score in 28 joints, and use of chloroquine, azathioprine and prednisone were adjusted for.

We are currently investigating CV risk and disease in consecutive RA patients seen in both a private and public care center<sup>16</sup>. The study was approved by the Ethics

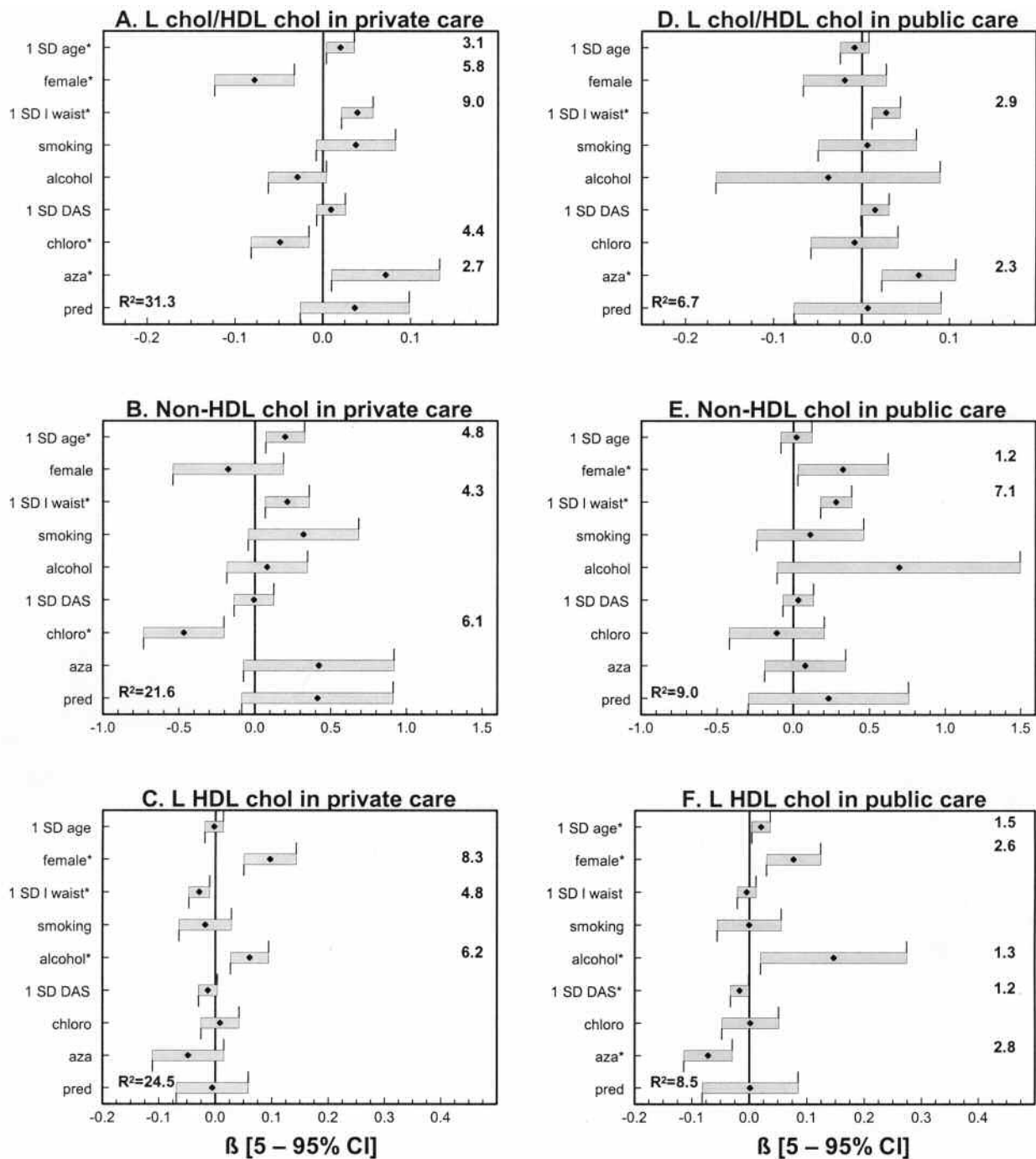


Figure 2. The associations of potential dyslipidemia risk factors with the atherogenic index, non-HDL cholesterol, and HDL cholesterol as assessed in multivariable regression models in private care (Panel A, B, C) and in public care patients (Panel D, E, F). The model R<sup>2</sup> are shown in the left lower corner of each panel. The values at the right side of each panel represent the partial R<sup>2</sup> for the significant associations ( $p < 0.05$ ) of dyslipidemia risk factors with lipid variables. L: logarithmically transformed (applied when characteristics were non-normally distributed); chol/HDL chol: total cholesterol/HDL cholesterol ratio; 1 SD: increase of one standard deviation; DAS: Disease Activity Score in 28 joints; chloro: chloroquine; aza: azathioprine; pred: prednisone. \*Characteristics significantly associated with lipid variables.

Committee for Research on Human Subjects of the University of Witwatersrand and informed written consent is obtained from each participant. Table 1 shows potential dyslipidemia risk factors including demographic and

lifestyle characteristics, abdominal adiposity, RA disease activity, and drug therapy in the 626 subjects studied so far. Their mean (SD) disease duration was 9.2 (2.4) years and did not differ by healthcare setting ( $p = 0.6$ ). Strikingly,

most risk factors differed markedly between public and private care patients. Public care patients were more often women and Black and less often European, smoked and used alcohol less frequently, had a higher waist circumference and higher disease activity, and used more DMARD. Figure 1 shows the atherogenic indices as well as proatherogenic and antiatherogenic cholesterol. Public care patients experienced lower antiatherogenic cholesterol levels, and this association was explained by dyslipidemia risk factors. The atherogenic index was similar in both groups in univariate and multivariable analyses. Figure 2 shows the independent associations of potential dyslipidemia risk factors with the 3 studied lipid variables in private and public care patients. Since 541 (86%) patients were using combination DMARD, we first assessed the association of DMARD with the atherogenic index in all patients in a multivariable regression model in which all DMARD were entered as independent predictors. This revealed that only azathioprine and chloroquine were associated with dyslipidemia (data not shown) and therefore, these were the DMARD entered in the models in Figure 2. Notably, overall, except for smoking status and prednisone use, each dyslipidemia risk factor was associated with at least one lipid variable. Although lipoprotein concentrations did not differ in private and public care patients (Figure 1), the overall contribution of the studied risk factors was up to 4.7-fold higher in private care patients as compared to public care patients (see model  $R^2$  data in Figure 2). Whether this finding implicates the presence of an enhanced adverse effect of psychosocial stress on lipids in socioeconomically disadvantaged patients with RA deserves further study. The association of age and gender with lipoproteins in private care patients was similar to that reported in the general population<sup>14</sup>, whereas the respective characteristics were not associated with the atherogenic index in public care patients. Abdominal adiposity most strongly predicted lipoprotein concentrations. This was due to an adverse association with both proatherogenic and antiatherogenic cholesterol concentrations in private care patients. In public care patients, however, abdominal adiposity predicted the atherogenic index solely by an adverse association with proatherogenic cholesterol. In contrast to what is reported in untreated RA<sup>2-4</sup>, disease activity was weakly associated with antiatherogenic cholesterol, and only in public care patients, and disease activity was not significantly associated with the atherogenic index in both the public and private care patients. Chloroquine is an effective inhibitor of 2,3 oxidosqualene cyclase whereby it reduces cholesterol synthesis<sup>17</sup>. Chloroquine was associated with reduced proatherogenic cholesterol and a lower atherogenic index in private care patients, but this was not seen in public care patients. Finally, azathioprine, an agent that was relatively commonly used in our patients due to the suboptimal access and inaccessibility to biological agents in our private care and public care setting, respectively, was consistently

associated with increased atherogenic indices, a previously unreported complication of this therapy. In contrast to Garcia-Gómez, we found no association of prednisone with lipids, presumably because its use is much more limited in our settings (Table 1). In further multivariable analyses, the consideration of exercise in private care patients and race as well as statin therapy in both private and public care patients did not reveal an association of these factors with lipoproteins and did not affect the associations, as shown in Figure 2 (data not shown).

In conclusion, the study by Garcia-Gómez indicates that the excess in CVD in treated established RA may not be attributable to an excess in dyslipidemia. However, dyslipidemia does participate in RA atherogenesis even when the disease is treated with DMARD<sup>18,19</sup>, and its determinants comprise more of the conventional dyslipidemia risk factors than of RA characteristics. The association of dyslipidemia risk factors with lipoproteins further differs markedly by socioeconomic status in RA. Conventional dyslipidemia risk factors and socioeconomic status should therefore be considered in future studies aimed at elucidating dyslipidemia in RA. Last but not least, lifestyle factors and excess abdominal adiposity should be addressed in the assessment and management of lipoprotein-induced CVD risk in RA and lipoprotein concentrations should be monitored when DMARD therapy is altered.

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