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LIPID PARADOX IN RHEUMATOID ARTHRITIS: THE IMPACT OF SERUM LIPID MEASURES AND SYSTEMIC INFLAMMATION ON THE RISK OF CARDIOVASCULAR DISEASE

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Abstract

Objectives—To examine the impact of systemic inflammation and serum lipids on cardiovascular disease (CVD) in rheumatoid arthritis (RA).

Methods—In a population-based RA incident cohort (1987 ACR criteria first met between 1988 and 2007), we collected serum lipid measures, erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) measures and cardiovascular events including ischemic heart disease, and heart failure. Cox models were used to examine the association of lipids and inflammation with the risk of CVD and mortality adjusting for age, sex and year of RA incidence.

Results—The study included 651 RA patients (mean age 55.8 years, 69% female); 67% were rheumatoid factor positive. ESR was associated with the risk of CVD (hazard ratio [HR] 1.2 per 10 mm/hr increase, 95% confidence interval [CI] 1.1, 1.3). Similar findings, although not statistically significant, were seen with CRP (p=0.07). We found a significant nonlinear association for total cholesterol (TCh) on risk of CVD, with 3.3-fold increased risk for TCh<4 mmol/L (95%CI 1.5, 7.2) and no increased risk of CVD for TCh≥4 mmol/L (p=0.57). Low low-density cholesterol (LDL<2 mmol/L) was associated with marginally increased risk of CVD (p=0.10); there was no increased risk for LDL≥2 mmol/L (p=0.76).

Conclusion—Inflammatory measures (particularly, ESR) are significantly associated with the risk of CVD in RA. Lipids may have paradoxical associations with the risk of CVD in RA, whereby lower TCh and LDL levels are associated with increased cardiovascular risk.

Keywords

rheumatoid arthritis; inflammation; lipid paradox; cardiovascular outcomes; ESR; CRP; lipids

Introduction

Adverse lipid profile or dyslipidemia is an important risk factor for cardiovascular disease (CVD) in the general population [1,2]. Several studies reported a continuous increase in cardiovascular risk with increasing serum cholesterol levels [3,4]. The evidence for the excess cardiovascular risk in patients with rheumatoid arthritis (RA) subjects is convincing

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[5–7]. However, the association between lipids and cardiovascular risk in RA appears to be more complex than in the general population, with systemic inflammation being a notable contributor to the lipid profile changes [8]. Growing evidence suggests that patients with active untreated RA have reduced total cholesterol (TCh), low-density cholesterol (LDL) and high-density cholesterol (HDL) levels [8–12]. In contrast, declines in inflammation may coincide with increases in serum lipid values [11,13–15]. The implications of these changes on cardiovascular risk are unclear, and the relative impact of systemic autoimmune inflammation and dyslipidemia on cardiovascular risk in RA is not fully understood. We sought to examine the impact of systemic inflammation and serum lipids on the development of CVD in RA.

Methods

Study setting and design

Using the population-based resources of the Rochester Epidemiology Project (REP) medical records linkage system, we performed a retrospective cohort study. The unique features of the REP and its potential for population-based studies were previously described [16–18]. In brief, this system allows ready access to the complete in-patient and out-patient medical records of Olmsted County, Minnesota residents from all health care providers from the Mayo Clinic, its affiliated hospitals and the Olmsted Medical Center. REP resources ensure virtually complete ascertainment of all clinically recognized cases of RA among the residents of Olmsted County.

We studied a population-based incidence cohort of RA patients who were Olmsted County, Minnesota residents ≥18 years of age and first fulfilled the 1987 American College of Rheumatology (ACR) criteria [19] between 1/1/1988 and 1/1/2008. The date when the patient fulfilled ≥4 ACR criteria for RA was considered the RA incidence date. From the original medical records, we collected data on age, sex, rheumatoid factor (RF) positivity, antirheumatic medications (methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs [DMARDs], biologic response modifiers and corticosteroids) and lipid-lowering medications (statins and other lipid-lowering drugs). The results of all clinically performed erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) measures and fasting serum lipid measures including TCh, LDL, HDL and triglycerides (TG) were also abstracted from the medical records. According to the Mayo Clinic laboratory reference ranges, increased ESR was defined as >29 mm/hr for females and >22 mm/hr for males and increased CRP was defined as >8 mg/L for both genders. Abnormal lipid levels were defined according to the Adult Treatment Panel III (ATPIII) guidelines [2] as TCh≥6.2 mmol/L (≥240 mg/dL), LDL≥4.1 mmol/L (≥160 mg/dL), TG≥2.3 mmol/L (≥200 mg/dL) or HDL<1.0 mmol/L (<40 mg/dL), and according to the European Society of Cardiology (ESC) guidelines [20] as TCh≥5.0 mmol/L (≥193 mg/dL), LDL≥3.0 mmol/L (≥116 mg/dL), TG≥1.7 mmol/L (≥151 mg/dL) or HDL<1.0 mmol/L (<40 mg/dL). All lipid measures are further given in mmol/L. To convert from mmol/L to mg/dL, multiply TCh, LDL and HDL levels by 38.67, and TG levels by 88.57.

Information on cardiovascular risk factors was collected according to standard guidelines as previously described [21]: family history of premature ischemic heart disease (IHD) if IHD was present in first degree relatives at age <65 females and <55 males; smoking (never, current or former); hypertension (defined as ≥2 ambulatory blood pressure readings ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic obtained during a 1-year period, physician diagnosis or documented use of antihypertensive medications); body mass index (BMI) at baseline and diabetes mellitus (defined as fasting plasma glucose ≥126 mg/dl [≥7.0 mmol/l] physician diagnosis or documented use of insulin and/or oral hypoglycemic agents).

CVD was defined as the earliest of the following incident events: IHD (including angina, hospitalized myocardial infarction [MI], or revascularization procedures, i.e., coronary bypass surgery or angioplasty) or heart failure (HF) from any cause according to Framingham criteria [22,23]. We also analyzed HF and all-cause mortality separately. The study protocol was approved by the Institutional Review Boards from Mayo Clinic and Olmsted Medical Center.

Statistical Methods

Descriptive statistics (means, percentages, etc.) were used to summarize inflammatory and lipid measures. Cox proportional hazard models stratified by sex with age as the time scale were used to examine the association of inflammatory and lipid measures with the risk of CVD using smoothing splines (i.e. smooth non-linear curve fit through the data) to examine possible non-linear effects [24,25]. Patients with a cardiovascular event before RA were excluded from subsequent analyses as they were not at risk of developing that cardiovascular event during follow-up. Models adjusted for traditional cardiovascular risk factors (including family history of premature IHD, smoking, hypertension, diabetes mellitus, BMI≥30 kg/m^2) and low BMI (BMI<20 kg/m^2) were also examined. Time-dependent covariates were used to represent inflammatory and lipid measures during follow-up as their values changed each time they were measured clinically. Cumulative inflammatory burden (sometimes referred to as “area under the curve”) was estimated by applying the most recent ESR value to each day of follow-up and summing these ESR values. Inflammatory burden was analyzed continuously using smoothing splines to allow for non-linear effects and was also categorized into tertiles. Cumulative inflammatory burden was not analyzed using CRP as only 20% of patients had CRP measures at RA incidence, since CRP was not routinely measured prior to the late 1990’s.

Results

The study included 651 incident patients with RA, of which 69% were female and 67% were RF positive (Table 1). Mean age at RA incidence was 55.8 years and the mean follow-up time was 7.8 years. Nearly all (96%) patients had ≥1 ESR measure and 71% had ≥1 CRP measure at some time during the follow-up. Lipid measures were available for 567 (87%) of patients. The majority of patients had abnormal measures of inflammatory markers at some time during the follow-up. Hypertension and obesity were the most common cardiovascular risk factors, followed by family history of IHD, smoking habit and diabetes mellitus. According to the ATPIII cut-offs, more than one third of patients had abnormal lipid levels at some time during the follow-up. These percentages were even higher according to the ESC cut-offs (Table 1). Nearly one third of patients were treated with lipid-lowering drugs, including statins. Most patients were treated with DMARDs and corticosteroids. About one fifth of patients used biologic response modifiers, of which the majority (95%) were anti-tumor necrosis factor-alpha agents.

During follow-up, 111 patients died, 62 developed IHD (including 24 patients who were hospitalized for MI), 56 patients developed HF. Accounting for the overlap, 82 patients developed one or more CVD events.

Associations of inflammatory and lipid measures with cardiovascular outcomes and mortality

Table 2 shows the associations of inflammatory and lipid measures with cardiovascular outcomes and mortality in RA. Increased ESR was associated with significantly increased risk of CVD, particularly, HF, and mortality adjusting for age, sex, and year of RA diagnosis. CRP was significantly associated with the risk of HF and mortality, and the

association of CRP with CVD approached statistical significance (p=0.07). Cumulative inflammatory burden of ESR was significantly associated with mortality. Patients in the middle or upper tertiles of inflammatory burden had a 5–7 fold increase in the risk of mortality compared to those in the lower tertile (p<0.001). Inflammatory burden of ESR in the middle and upper tertiles was also associated with a 2–3 fold risk of CVD (p<0.001). These associations persisted, but were somewhat attenuated, following additional adjustment for traditional cardiovascular risk factors and the use of lipid-lowering and antirheumatic drugs. For instance, the risk of mortality was increased 4–5 fold for patients in the middle or upper tertiles of inflammatory burden of ESR and the risk of CVD was increased 2-fold, but no longer reached statistical significance.

Regarding the associations between lipid measures and outcomes, only TG demonstrated the usual relationship, whereby increasing levels of TG were significantly associated with CVD (Table 2). Paradoxically, both lower TCh and higher HDL were significantly associated with the risk of HF. These associations persisted after additional adjustment for traditional cardiovascular risk factors. The associations were similar in RF positive versus RF negative patients and in statin-users versus non-users (data not shown).

Examination of non-linear trends revealed a significant nonlinear association for TCh and risk of CVD. Figure 1 (upper panel) shows the hazard ratios for CVD according to TCh. The risk of CVD was increased for lower TCh measures. For TCh<4 mmol/L, the risk of CVD increased by 3.27 per 1.0 mmol/L decrease in TCh (95% CI 1.48, 7.24). However, there was no apparent change in cardiovascular risk for TCh≥4 mmol/L (p=0.57). A similar association was found for LDL with marginally increased risk of CVD for LDL<2 mmol/L (HR 2.55 per 1 mmol/L decrease in LDL, 95% CI 0.83, 7.84, p=0.10) and no apparent change in cardiovascular risk for LDL≥2 mmol/L (p=0.76) (Figure 1, lower panel). In total 5% of patients had TCh levels <4 mmol/L and 4% had LDL<2 mmol/L at some point during the follow-up. A similar relationship of LDL with the risk of MI was also observed (i.e., lower LDL values were associated with higher risk of MI; p=0.05).

Interactions between inflammatory and lipid measures on cardiovascular outcomes

Interactions between lipids and inflammatory measures on the risk of CVD were examined. We found significant interactions between LDL and ESR for the risk of CVD (interaction p=0.048). Figure 2 shows hazard ratios for CVD in RA for various levels of ESR according to LDL levels. The hazard ratio of CVD increased dramatically as ESR rose above 30 mm/hr. Of note, the impact of LDL on cardiovascular risk differed depending on the ESR level, whereby LDL appeared to have more impact on the risk of CVD at higher ESR (i.e., ESR>30 mm/hr). Indeed, among patients with ESR>30 mm/hr, the risk of CVD was higher in those with LDL<2 mmol/L (e.g. LDL=1.5 mmol/L) versus LDL≥2 mmol/L. Likewise, the impact of LDL on cardiovascular risk differed depending on the CRP level (interaction p=0.04). However, LDL appeared to have more impact on the risk of CVD at lower CRP levels (i.e., CRP<25 mg/L), whereas LDL did not substantially change the risk of CVD when CRP is high (CRP≥25 mg/L).

Interactions between inflammatory measures and lipid atherogenic ratios on the risk of CVD were also examined. Figure 3 (upper panel) shows hazard ratios for the association between ESR and TCh/HDL on the risk of CVD. Patients with ESR>30 mm/hr and a TCh/HDL=2 had a higher risk of CVD than those with TCh/HDL=4. In contrast, patients with TCh/HDL=6 had a lower risk of CVD than those with TCh/HDL=4. Figure 3 (lower panel) shows the same analyses with CRP instead of ESR. Similarly, in patients with higher CRP (i.e., CRP≥25 mg/L), lower TCh/HDL ratio was associated with higher cardiovascular risk compared to those with higher TCh/HDL ratio (interaction p=0.02). Similar findings were found with the LDL/HDL ratios.

To explore the impact of lipid-lowering drugs on the association of lipids and inflammation with study outcomes, the interactions between lipid-lowering drug use and the variables in table 2 (i.e. inflammatory and lipid measures) on CVD and mortality were examined, and no statistically significant associations were found ($p>0.2$ for all). Interaction of antirheumatic medications (i.e. methotrexate, hydroxychloroquine, other DMARDs, biologic response modifiers and corticosteroids) with inflammatory and lipid measures on CVD and mortality were also examined, and no statistically significant associations were found. However, our study may be underpowered to detect these complex relationships.

Discussion

This study reports the association of inflammatory and lipid measures with CVD and mortality in RA. Using a population-based incidence cohort of RA patients, we demonstrated that inflammatory measures, particularly ESR, were significantly associated with CVD and mortality after adjustment for cardiovascular risk factors and medication use. We found paradoxical associations between TCh and LDL levels, as well as TCh/HDL and LDL/HDL ratios and CVD in RA, whereby patients with lower TCh and LDL levels and lower atherogenic ratios had increased risk of CVD. Furthermore, we have shown significant interactions between LDL and ESR for the risk of CVD, suggesting that the associations of lipids with CVD in RA may be confounded by inflammation.

Our findings underscore the importance of systemic inflammation as a key player in the development of CVD in RA by demonstrating independent associations of ESR and CRP with cardiovascular outcomes and mortality. This is concordant with the concept of acceleration of cardiovascular risk and mortality with increasing inflammatory burden and suggests the need for minimization of cumulative inflammation in RA [26–28]. While lipids levels are known to be associated with CVD in the general population, the AMORIS study found this association between TCh and acute MI was much weaker among RA patients [29]. Similarly, associations between increasing lipid levels and outcomes in RA in our study were not apparent. In fact, we found increased risks for cardiovascular outcomes with low TCh and LDL suggesting the traditional interpretation of hypercholesterolemia as a risk factor for CVD may not apply in RA[30]. These relationships corroborate the concept of reverse epidemiology, whereby low levels of traditional risk factors (i.e., lipids, BMI and systolic blood pressure) can appear deleterious [31–33]. In RA, paradoxical associations have been previously demonstrated between low BMI and increased cardiovascular and all-cause mortality[33–35].The association of low lipid levels with adverse outcomes has also been reported in the elderly and in patients with HF, IHD, and cancer [31,33,36–40].

While lipids may directly confer protective effects by modulating autoimmune and inflammatory markers, other underlying mechanisms, primarily the cholesterol-lowering effect of systemic inflammation, may contribute [31,41–44]. Concordantly, we have detected interactions of inflammatory measures with LDL and lipid atherogenic ratios showing that the impact of lipid measures differed depending on the levels of inflammatory markers. The CARRE study recently found the associations between lipid measures and CVD were more apparent in the setting of elevated CRP [45]. Unlike th is study showing marginally increased risk of CVD in RA patients with increased TCh/HDL ratios and elevated CRP, in our study lower TCh/HDL ratios were significantly associated with increased risk of CVD in patients with elevated inflammatory measures. These findings are not necessarily contradictory, as both studies suggest that inflammation may modulate the impact of lipid measures on CVD. The difference in the results could be explained by changes in the impact of inflammation on the association between lipids and CVD at different levels of disease activity, or by other factors including RA duration and comorbidities. In fact, the mechanisms by which inflammation confounds the association of

cholesterol and CVD are unclear. In particular, it is unclear why the impact of LDL on the risk of CVD differed for ESR and CRP. This discrepancy may be associated with differences in the relationships between lipids and ESR versus lipids and CRP, which may stem from some important distinctions between ESR and CRP [46]. ESR increases with age and changes relatively slowly, whereas CRP changes rapidly and has a broader range of abnormal values, suggesting that they represent different aspects of inflammation [47]. In fact, ESR and CRP have been reported to have only moderate correlation (r=0.59) and this is similar in our cohort (r=0.56)[48]. While the nature of the interaction of inflammatory markers with lipids on the risk of CVD requires further elucidation, it appears clear that the impact of inflammation on cardiovascular risk in RA is pivotal. Given that the majority of RA patients manifest with increased levels of inflammatory markers, and sustained inflammation is prevalent even in “well-controlled” RA, the interaction of inflammatory markers with lipids and modification of cardiovascular risk may be common in RA [49]. Thus, our findings and others underscore the importance of interpretation of lipid levels in the context of inflammatory activity in persons with RA [45,46]. Furthermore, our findings point to the need for definition of the therapeutic goals for lipid-lowering drugs in RA considering not only serum lipids but also the inflammatory milieu. This is concordant with the emerging evidence for the benefits of dual targeting of lipids and inflammation in RA [12,50,51]. Indeed, the benefits of statin use in patients with low cholesterol levels, but increased CRP levels have been demonstrated in the general population [12]. The anti-inflammatory properties of statins may explain these benefits, raising a possibility of advantages of statin use in RA [52]. In our study there was no apparent difference between statin-users versus non-users for the association of lipids and outcomes. However, the role of statins in the association between lipids and outcomes needs further investigation.

Our study has several potential limitations. From this observational study, we cannot draw any causal relationship between lipids, inflammation and outcomes, and prospective studies with long-term follow-up are needed. In our study inflammatory and lipid measurements were not always available on the same date. The fluctuations of inflammatory and lipid measures during the disease course could affect the associations of these measures with cardiovascular outcomes. However, in our analysis, we used the most recent lipid and inflammatory measures at each time point throughout follow-up, which we believe, minimized this weakness. As in any retrospective study, only information available from medical records was used to define the study outcomes including HF. Thus, we could not identify different etiological subsets of HF. However, we employed the Framingham criteria, the most commonly used and extensively validated approach to define HF from any cause. Finally, during the period of investigation the population of Olmsted County, Minnesota was predominantly white. Thus, the results may not be generalizable to non-white individuals.

This study has several important strengths. To the best of our knowledge, this is the first large longitudinal, population-based study showing a reverse relationship between lipids and cardiovascular outcomes in RA and defining inflammation as a potential confounder for this association. RA patients included in the study represent a large population-based incident RA cohort. The study takes advantage of the extensive follow-up data on inflammatory and lipid measures available through the REP. Because of the comprehensiveness of the available data, we were able to account for the large majority of potential confounders including cardiovascular risk factors, antirheumatic medications and lipid-lowering drugs.

In conclusion, our findings demonstrate that inflammatory measures, particularly ESR, are significantly associated with the risk of CVD in RA. The association between lipid measures and the risk of CVD in RA appears to be paradoxical, whereby lower TCh and LDL levels and lower atherogenic ratios are associated with increased cardiovascular risk. These

findings suggest that systemic inflammation in RA may interact with lipid measures to promote the development of CVD. More studies, especially, prospective studies with long-term follow-up, are needed to better understand the underlying biological mechanisms and clinical implications of these findings.

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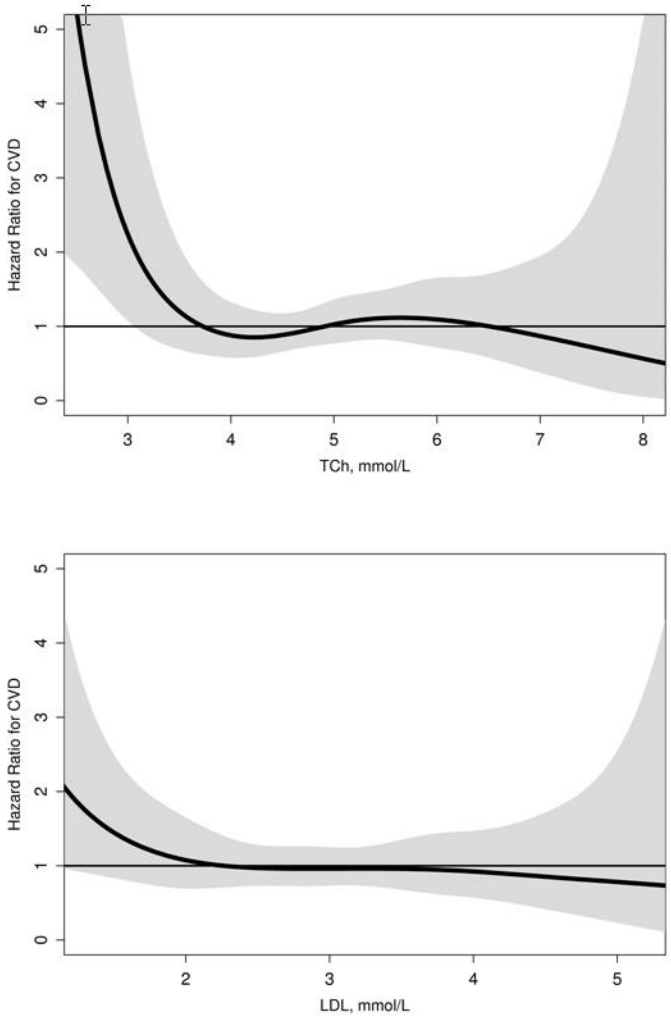

Figure 1.
Hazard ratios for CVD in RA (solid lines) according to TCh (upper panel) and LDL (lower panel). Shaded areas represent 95% confidence intervals.
Abbreviations: CVD = cardiovascular disease; RA = rheumatoid arthritis; TCh = total cholesterol; LDL = low density cholesterol.

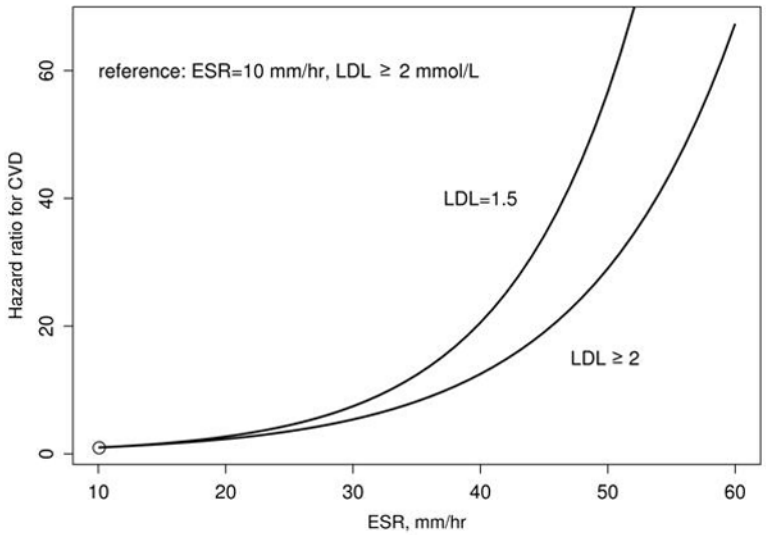

Figure 2.

Hazard ratios (HRs) for CVD in RA for various levels of ESR according to LDL levels. All HRs are related to the reference point (i.e. ESR=10 mm/hr and LDL≥2 mmol/L, where HR=1.0).

Abbreviations: CVD = cardiovascular disease; RA = rheumatoid arthritis; ESR = erythrocyte sedimentation rate; LDL = low density cholesterol.

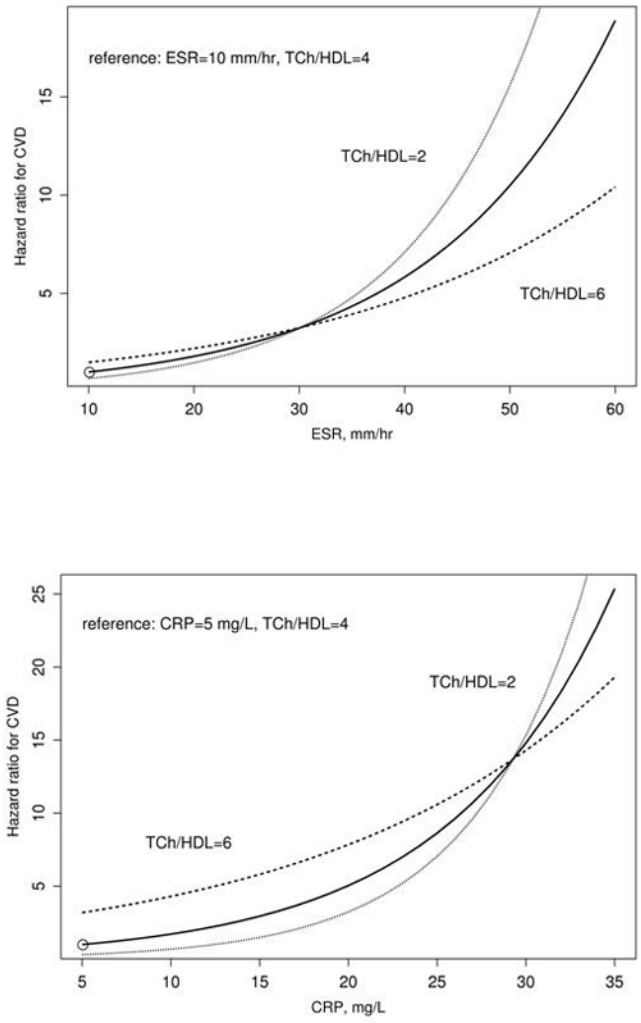

Figure 3.

Hazard ratios (HRs) for interactions of TCh/HDL ratio with ESR (upper panel) and CRP (lower panel) on the risk of CVD. Solid line shows the association between various ESR/CRP and CVD for TCh/HDL ratio=4. Dotted line and dashed line show the same associations for TCh/HDL ratios of 2 and 6, respectively. All HRs are related to the reference point (i.e. ESR=10 mm/hr and TCh/HDL=4, where HR=1.0). For TCh/HDL ratio=4, higher ESR/CRP measures are associated with increased risk of CVD (e.g. ESR=50 mm/hr is associated with approximately 10-fold increase in CVD risk)

Abbreviations: CV = cardiovascular; TCh/HDL = total cholesterol/high-density cholesterol ratio; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

Table 1

Characteristics of 651 incident RA patients (1988–2007, Olmsted County, Minnesota)

Variable	Value
Age at RA incidence, years, mean ± SD	55.8 ± 15.7
Length of follow-up, years, mean ± SD	7.8 ± 5.2
Female, n (%)	446 (69)
RF positive, ever, n (%)	433 (67)
% tested for RF, ever	99
Abnormal ESR, ever, n (%) (>29 mm/hr for females and >22 mm/hr for males)	405 (62)
Abnormal CRP, ever, n (%) (>8 mg/L)	316 (67)
Family history of IHD	150 (23)
Smoking at RA incidence, n (%)	
- current	120 (18)
- former	229 (35)
Hypertension, ever, n (%)	562 (86)
Obesity (BMI≥30 kg/m^2), ever, n (%)	323 (50)
Diabetes mellitus, ever, n (%)	116 (18)
Abnormal lipid measures, ever, n (%):	
According to the ATPIII guidelines	
- TCh (≥6.2 mmol/L)	234 (41)
- LDL (≥4.1 mmol/L)	195 (35)
- HDL (<1 mmol/L)	213 (38)
- TG (≥2.3 mmol/L)	208 (37)
According to the ESC guidelines	
- TCh (≥5 mmol/L)	436 (77)
- LDL (≥3 mmol/L)	425 (76)
- HDL (<1 mmol/L)	213 (38)
- TG (≥1.7 mmol/L)	313 (57)
Lipid-lowering drug use, ever, n (%)	209 (32)
Antirheumatic drug use, ever, n (%):	
- Methotrexate	404 (62)
- Hydroxychloroquine	400 (61)
- Other DMARDs	173 (27)
- Biologic response modifiers	125 (19)

Variable	Value
- Corticosteroids	519 (80)

Abbreviations: RA = rheumatoid arthritis; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IHD = ischemic heart disease; BMI = body mass index; ATPIII = Adult Treatment Panel III; ESC = European Society of Cardiology; TCh = total cholesterol; LDL = low-density cholesterol; HDL = high density cholesterol; TG = triglycerides; DMARD = disease-modifying antirheumatic drug

Table 2

Associations of inflammatory measures and lipid measures with cardiovascular outcomes and mortality [*#]

Outcome / *Measure*	CVD HR (95% CI)	Heart Failure HR (95% CI)	Mortality HR (95% CI)
Inflammatory measures [‡]			
ESR, mm/hr	**1.20 (1.11, 1.31)**	**1.23 (1.12, 1.35)**	**1.22 (1.14, 1.31)**
CRP, mg/L	1.10 (0.99, 1.22)	**1.25 (1.06, 1.48)**	**1.08 (1.01, 1.16)**
Inflammatory Burden [†]			
Lower ESR Tertile	1	1	**1**
Middle ESR Tertile	**2.44 (1.32, 4.48)**	1.28 (0.59, 2.76)	**5.84 (3.06, 11.1)**
Upper ESR Tertile	**3.48 (1.89, 6.43)**	2.28 (1.15, 4.53)	**7.19 (3.77, 13.7)**
(p-value)	**(p-value < 0.001)**	(p-value =0.055)	**(p-value < 0.001)**
Lipid measures			
TCh, mmol/L	0.96 (0.90, 1.02)	**0.92 (0.85, 0.99)**	0.96 (0.92, 1.02)
LDL, mmol/L	0.95 (0.88, 1.02)	0.95 (0.87, 1.04)	0.98 (0.93, 1.04)
HDL, mmol/L	1.13 (0.94, 1.35)	**1.35 (1.09, 1.68)**	1.10 (0.96, 1.27)
TG, mmol/L	**1.03 (1.00, 1.06)**	1.01 (0.97, 1.05)	0.99 (0.96, 1.02)
TCh/HDL	0.99 (0.78, 1.25)	1.12 (0.86, 1.46)	1.06 (0.88, 1.29)
LDL/HDL	0.89 (0.66, 1.20)	1.06 (0.77, 1.47)	1.07 (0.85, 1.35)

[*] adjusting for age, sex and year of RA incidence

[#] statistically significant associations (p<0.05) are shown in bold;

[‡] Hazard ratios for ESR are reported per 10 mm/hr increase, for CRP per 10 mg/dL increase

[†] Cumulative ESR tertiles defined as follows: lower tertile (0 – 15,000 mm/hr); middle tertile (15,001 – 45,000 mm/hr); upper tertile (45,001 mm/hr and greater). For each outcome the lower tertile is the reference group.

Abbreviations: CVD = cardiovascular disease; HR = hazard ratio; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; TCh = total cholesterol; LDL = low density cholesterol; HDL = high density cholesterol; TG = triglycerides.