Systematic review and meta-analysis of individual serum lipids and analysis of lipid ratios in ankylosing spondylitis and healthy control cohorts: significantly lower mean HDL-cholesterol level in ankylosing spondylitis cohorts

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Abstract

Objective

Ankylosing spondylitis (AS) is suspected to have increased risk of atherosclerosis and cardiovascular disease (CVD) mortality. This systematic review and meta-analysis aims to critically study serum lipids and lipoprotein ratios in AS compared to healthy control (HC) subjects and determine any significant difference.

Methods

English-language articles were systematically searched in PubMed, Ovid Medline, Embase (Medline records removed), and Scopus databases from 1970 to 2021. Random-effects model was used to pool results expressed as standardised mean difference (SMD) in the lipid outcomes. Lipid ratios of total ÷ HDL-C and the log_{10}(TG/HDL-C), i.e. atherogenic index of plasma (AIP), were analysed by histograms of differences in weighted means and weighted SDs between AS and HC exposure cohorts.

Results

The meta-analysis included a total of 68 articles, 47 from database search and 21 from reference reviews. Pooled Hedges' g effect size revealed no difference in mean total cholesterol, mean triglycerides, and mean LDL-C between AS and HC subjects. However, mean HDL-C was significantly ($p<0.001$) lower in AS than HC subjects, with pooled Hedges' g (SE) for HDL-C of -0.484 (0.092), with 95% mean CIs [-0.664, -0.305]. In comparing differences in AS minus HC weighted means of total HDL-C ratios, 8 values in HC were below the lowest ratio in AS.

Conclusion

Highly significantly lower HDL-C levels occurred in AS versus HC subjects. The lower HDL-C levels in AS than HC populations deserve further study and may be attributable to uninvestigated demographic, exercise capacity, or clinical manifestations.

Key words

ankylosing spondylitis, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory and deforming condition of the spine and sacroiliac joints (SIJs) (1). It is suspected to have increased cardiovascular disease (CVD) morbidity and mortality compared to the general population (2), but results are not consistent (3). Cardiovascular morbidity and mortality in AS are attributed to atherosclerosis secondary to inflammation (2) and structural changes in the heart (4). A 2011 systematic review and meta-analysis of 13 reports on CVD mortality in AS and control cohorts revealed a non-significant higher AS risk of myocardial infarction (5). The CVD mortality risk in AS was suspected due to either systemic inflammation or lower HDL cholesterol (HDL-C) levels (5); however, as this difference did not reach significance, it is challenging to draw strong conclusions. In a meta-analysis of community-based CVD prevention programs and cardiovascular risk factors, serum HDL-C levels were not improved with intervention strategies (6), indicating its unclear determinants.

The ratio of total to HDL (total÷HDL) cholesterol was believed to be a superior predictor of CVD than serum cholesterol by the Framingham study and was incorporated in its risk score (7). Taken alone, HDL-C was reported to be the most specific predictor of CVD incidence and mortality rates (8). A more recent indicator of CVD risk is the atherogenic index of plasma (AIP) (9). AIP is the log ratio of molar concentrations of plasma triglycerides (TG) to HDL-C ($\log_{10}$ TG÷HDL mmol/L) (9). Males tend to have a higher AIP ratio than females in accordance with their generally lower HDL-C levels (7, 10). After age adjustment, AIP quartiles correlated (p=0.013) with incident ischaemic heart disease in a large prospective cohort of non-diabetic Korean adult males (11). Baseline AIP quartiles were highly (p<0.001) correlated with multiple demographics, blood pressure, lipid, and C-reactive protein (CRP) risk indicators of CVD (11). The AIP as well as total cholesterol (TC)÷HDL-C ratios were compared in relation to carotid artery intima-media thickness (cIMT) in a cohort of 52 male AS and matched healthy controls (12). Only AIP significantly (p=0.002) associated with patients' cIMT and was an independent marker of subclinical atherosclerosis (12).

The primary aim of this meta-analysis is to determine if any individual serum lipid significantly differs in cross-sectional cohorts of AS *versus* healthy control (HC) subjects, and to determine any patterns in serum lipid ratio data between AS and HC worthy of further exploration. The secondary aim is to investigate if any significant lipid difference occurs independently or may be influenced by pre-defined clinical, demographic, or inflammatory moderators.

Methods

Subjects studied

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). Case subjects are adults reported with AS, including those with radiographic and non-radiographic axial spondyloarthritis (axSpA). The control subjects are healthy adults included in the AS articles. Neither group had reported CVD or therapy to reduce serum lipids. Only English-language cross-sectional or case–control observational articles are included which have the same lipid outcome data in AS and HC subjects. The Newcastle-Ottawa Scale (NOS) Quality Instrument was followed to establish acceptable quality of included articles. Case and control subjects were from the same clinical source and had similar medical record ascertainment of the serum lipid outcomes of interest. The aim of all included studies was comparative analysis of serum lipids in AS and HC subjects. Representativeness of AS and HC cohorts were acceptable without evidence of selection bias.

Flow chart of selected articles

The flow chart diagram (Supplementary Fig. S1) shows numbers of titles generated from medical literature database searches in PubMed and Embase (Medline records removed) during July (n=202) and October (n=24) 2021, extending from 1970 to October 2021. Of the 226 PubMed and Embase articles,

Table I. Random-effects models of differences in lipids of ankylosing spondylitis minus healthy control subjects

Serum lipids	*k*	Pooled Hedges' *g*	*SE*	95% CI	*p*-values	Cochrane's Q	I^2
Total cholesterol (mg/dL)	58	-0.133	.073	[-0.277, 0.011]	0.069	Q (*df* = 57) = 342.95***	86.6%
Triglycerides (mg/dL)	61	-0.013	.059	[-0.103, 0.130]	0.825	Q (*df* = 60) = 293.73***	80.3%
High density lipoprotein (HDL) cholesterol (mg/dL)	59	-0.484	.092	[-0.664, -0.305]	<.001	Q (*df* = 58) = 486.77***	91.5%
Low density lipoprotein (LDL) cholesterol (mg/dL)	56	0.015	.096	[-0.173, 0.203]	0.876	Q (*df* = 55) = 463.59***	92.2%

K: number of independent cohort samples; pooled Hedges' *g*: pooled standardised mean difference or *g*; *SE*: standard error; CI: confidence interval; Cochrane's Q: observed variation; *df*: degrees of freedom; I^2 : percentage variation across studies due to heterogeneity. ***p<0.001.

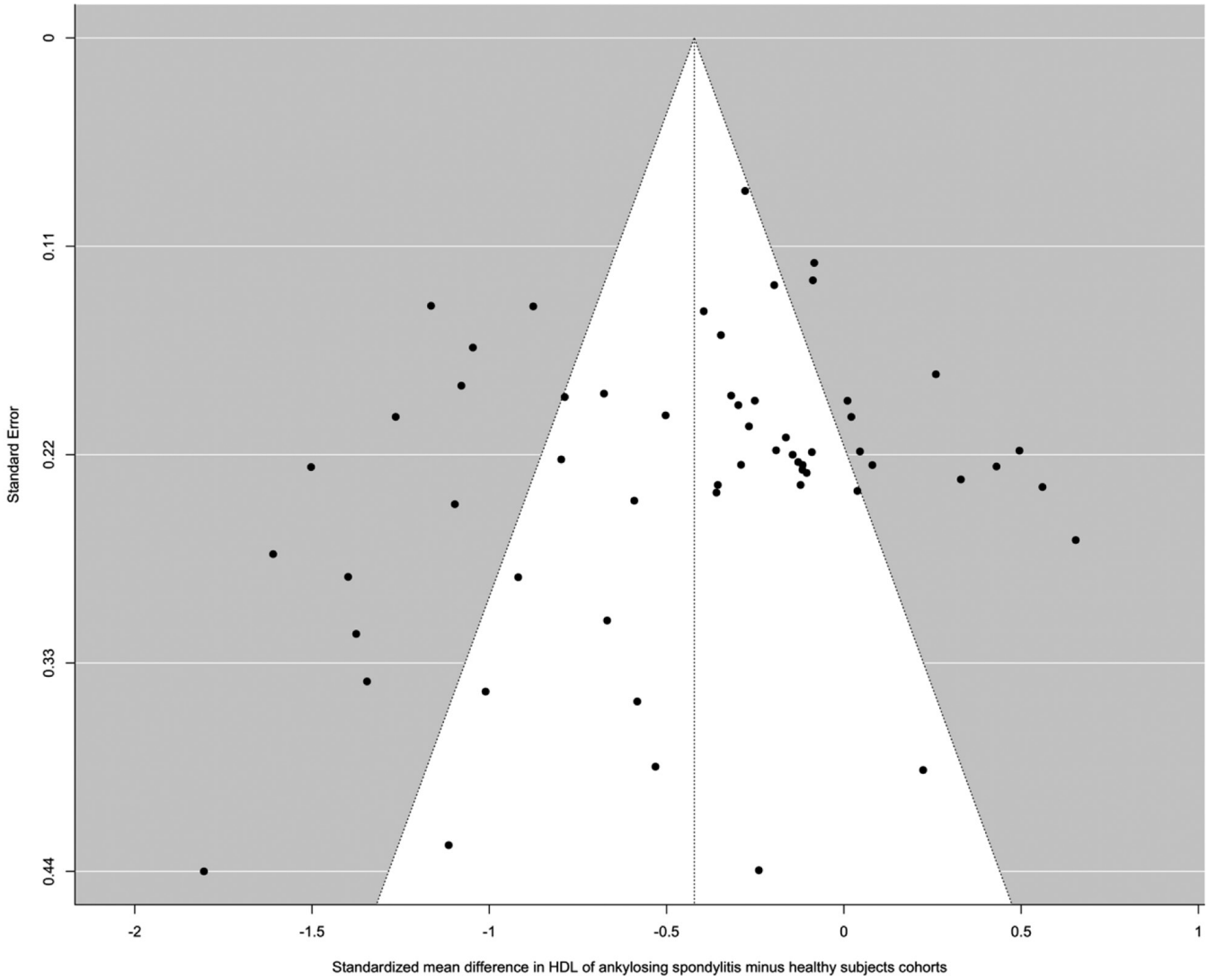

Fig. 1. Funnel plot of SMD in HDL-C of AS minus HC subjects after excluding outlier (Sakyi SA *et al*., 2012).

163 were excluded. In October 2021, OVID Medline and Scopus databases were separately searched, yielding 19 additional non-duplicate titles, of which 17 were excluded. Database searches yielded a total of 65 full-text articles, which were further assessed for eligibility. Full text articles were reviewed if an abstract did not definitively specify required data for eligibility. Of the 65 full-text articles assessed for eligibility, 17 were excluded, yielding 48 eligible database articles. These 48 accepted database articles included 1,960 references, which generated an additional 95 titles for full-text review. Twenty articles from references were subsequently identified as eligible for inclusion in the meta-analysis, yielding a total of 68 articles (16-83) (Suppl. Fig. S1).

All reference searches used the following key terms: "ankylosing spondylitis" or "spondylitis" or "spondylitides" or "spondyloarthritis" or "spondylarthritis"; and "cholesterol (C)" or "triglycerides (TG)" or "high-density lipoprotein (HDL) cholesterol" or "low-

density lipoprotein (LDL) cholesterol" or "lipoproteins" or "serum lipids." English-language articles were selected for inclusion if the same lipid data were reported in both AS and HC subjects. Cohorts were excluded with high-risk CVD or statin usage in all subjects as well as articles investigating medical conditions that affect lipid profiles. A summary listing was composed of all selected variables for analyses in accepted cohorts (*i.e*. Master Lipid Summary Table). A separate Coding Sheet was composed with columns for all variables selected for analyses. The Master Summary and Coding Sheets are available on request from the corresponding author.

Funding for the study was derived from a rheumatology research account at the University of Illinois Foundation. The authors (MLB, SLF, and ATM) reviewed and assessed the eligibility of selected articles. Yan Cen, SLF, and ATM listed reasons for excluding articles evaluated from the abstract or full text review (Suppl. Fig. S1).

The extracted data are: lead author; report year; mean (SD) ages of AS and HC; mean (SD) duration of AS; healthy status of HC; country and continent of report; total number of AS and HC; total numbers and percentages of AS having tumour necrosis factor inhibitor (TNFi) therapy; numbers of AS and HC by gender; percentage of females; mean (SD) of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of AS subjects; means (SDs) of total cholesterol (C); TG; LDL-C; HDL-C; derived ratio of TC ÷ HDL-C; derived atherogenic index of plasma [(AIP), ($\log_{10}$TG ÷ HDL-C mmol/L)]; erythrocyte sedimentation rate [(ESR), mm/hr], and C-reactive protein [(CRP), mg/L].

Mean (SD) data were compared between AS and HC cohorts. In a minority of articles, when median and range or interquartile range (IQR) were reported, the mean (SD) was estimated according to the formulas of Hozo *et al*. (14). When lipid data were presented as mmol/L, values were converted to mg/dL. A pre-formatted Excel Coding Sheet was prepared for entry of all variables by two medical student coders (EOR and AP) independently and with confirmation of accuracy.

Statistical analysis

Summary effect size estimates and the corresponding 95% CIs were calculated using random-effects models. The statistical heterogeneity of meta-analysis was assessed using the I^2 statistic. Pre-defined subgroup analyses were conducted by selected study-level characteristics, *e.g*. study location (Europe, Turkey, or other origins), sex (percentage females), or source of article (database *vs*. reference search). Forest plots were produced to graphically display the results of the individual studies along with the summary estimates based on the models. The differences in AS minus HC values of inflammatory metrics (X-coordinate) and lipids (Y-coordinate) were correlated using meta-regression models. The bubble plots were produced to graphically display the mixed-effects meta-regression model results, as in the study of Jayedi *et al*. (15). Funnel plots were visually inspected for asymmetry and underwent Egger's test for asymmetry. Leave-one-out sensitivity analysis was carried out by sequentially omitting individual studies to explore whether the results were significantly influenced by a specific study. Outliers and influential cases were identified using deletion diagnostics. Externally standardised residuals were used to check the outliers; DFFITS (difference in fits), Cook's distance, and hat values were used to identify the influential cases. A case may be considered to be "influential" if at least one of the following is true: (1) the absolute DFFITS value is larger than 3*SQRT(p/(k-p)), where p is the number of mode coefficients and k is the number of studies; (2) the lower tail area of a chi-square distribution with p degrees of freedom cut off by the Cook's distance is larger than 50%, (3) the hat value (diagonal elements of the hat matrix) is larger than 3*(p/k). A study may be considered influential if its exclusion from the analysis leads to considerable changes in the fitted model. The accepted 68 articles (16-83) are listed in References in essentially chronologic order. This meta-analysis of serum lipids was performed using the "metafor" package version 3.4-0 in R version 4.1.2.

Meta-analysis of the TG/HDL-C ratio in the general population revealed a significantly higher risk of CV events in participants with the highest ratio, compared to those with the lowest TG/HDL-C ratio (84). Meta-analyses of the ratio of 2 random variables, like $\log_{10}$ (TG/HDL-C), do not yield reliable results (85-87), unless the denominator mean is high compared to its variance and the ratio does not cross zero (85). The preceding qualifications (85-87) determined that weighted means (SDs) be used in analysis of the ratios of total ÷ HDL-C and $\log_{10}$ (TG/HDL-C) in AS *versus* HC subjects. To examine lipid ratios across studies, the total cholesterol divided by the HDL-C value was derived from each study as a group function (7). These data were also log transformed to derive AIP (9). Because the original studies did not report these ratios, the variance of each ratio could not be determined. As such, only descriptive statistics (means, standard deviations) were obtained for the ratios of AS and HC cohorts. Histograms of the weighted averages of the ratios were calculated along with weighted standard deviations to account for the differences in sample size of the groups across cohorts.

Results

This meta-analysis included 68 articles (16-83) with the same lipid data on AS and HC subjects in 56 to 61 cohorts (Table I, column k). Mean total cholesterol, mean TG, and mean LDL-C did not differ significantly between AS and HC subjects. However, the pooled Hedges' g for HDL-C of -0.484, with standard error (SE) of 0.092, and 95% CIs (-0.664, -0.305), reflects highly (p<0.001) significantly lower mean HDL-C values in AS than HC subjects. Cochrane's Q percentage heterogeneity was highly significantly different in all lipids, ranging from 80.3 (TG) to 92.2 (LDL-C). One study (41), Sakyi SA *et al*., 2012, was identified as an influential HDL-C case. After excluding this case, the conclusion regarding significantly lower HDL-C in AS than HC subjects remained the same, with the pooled Hedges' g of

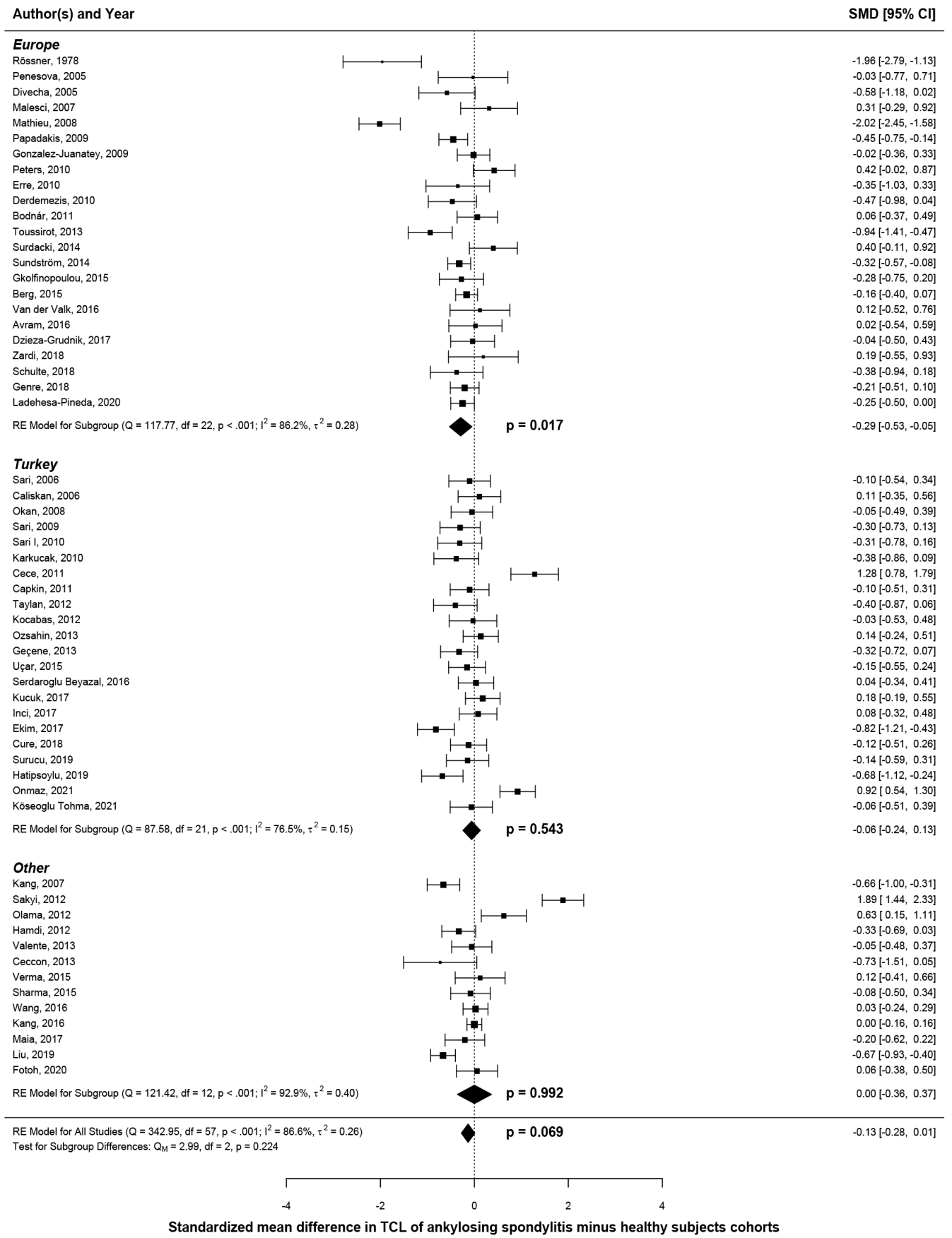

Fig. 2. Forest plot and subgroup analysis of total cholesterol by Geographic Regions.

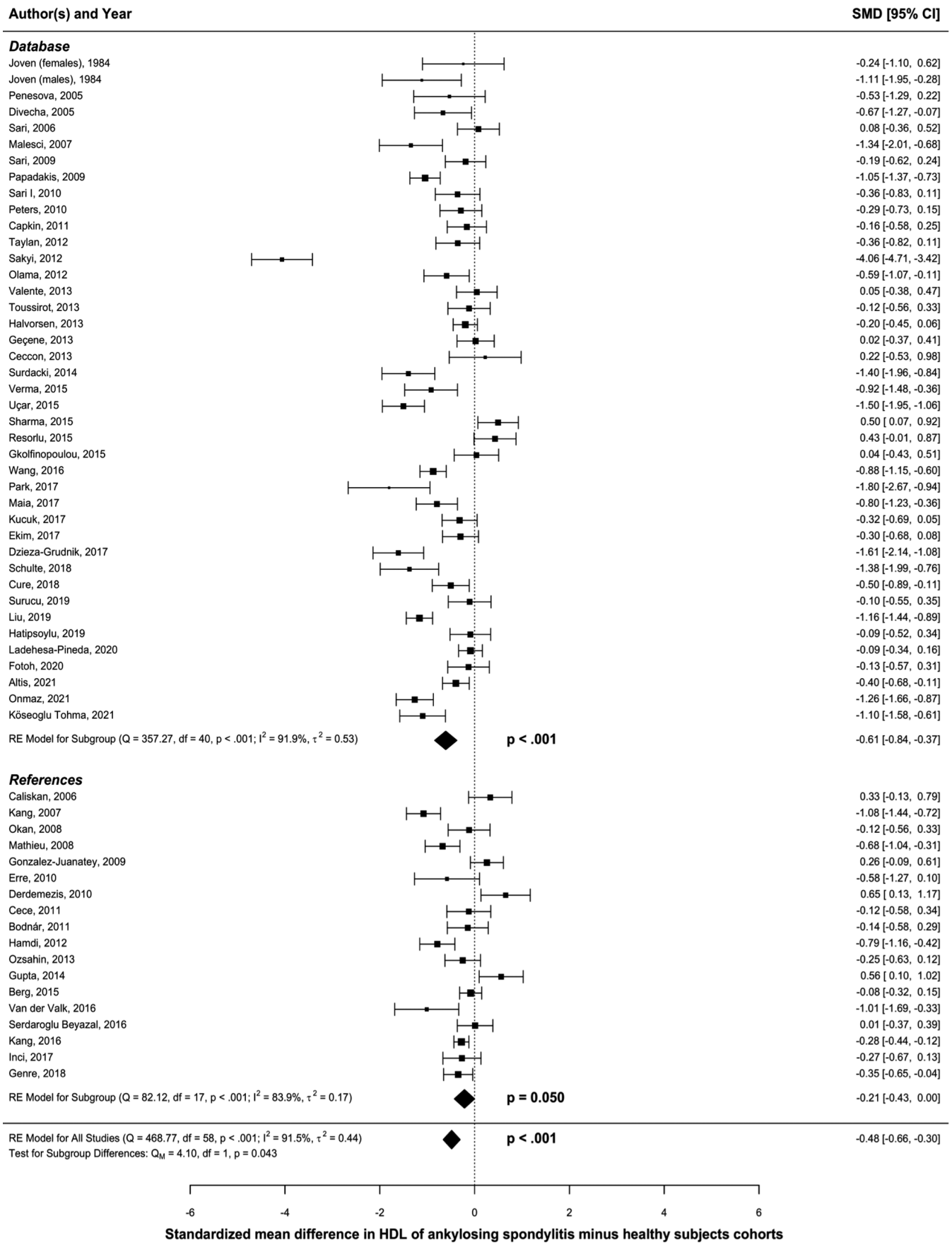

Fig. 3. Forest plots for the subgroup analysis of HDL-C according to the Article Source.

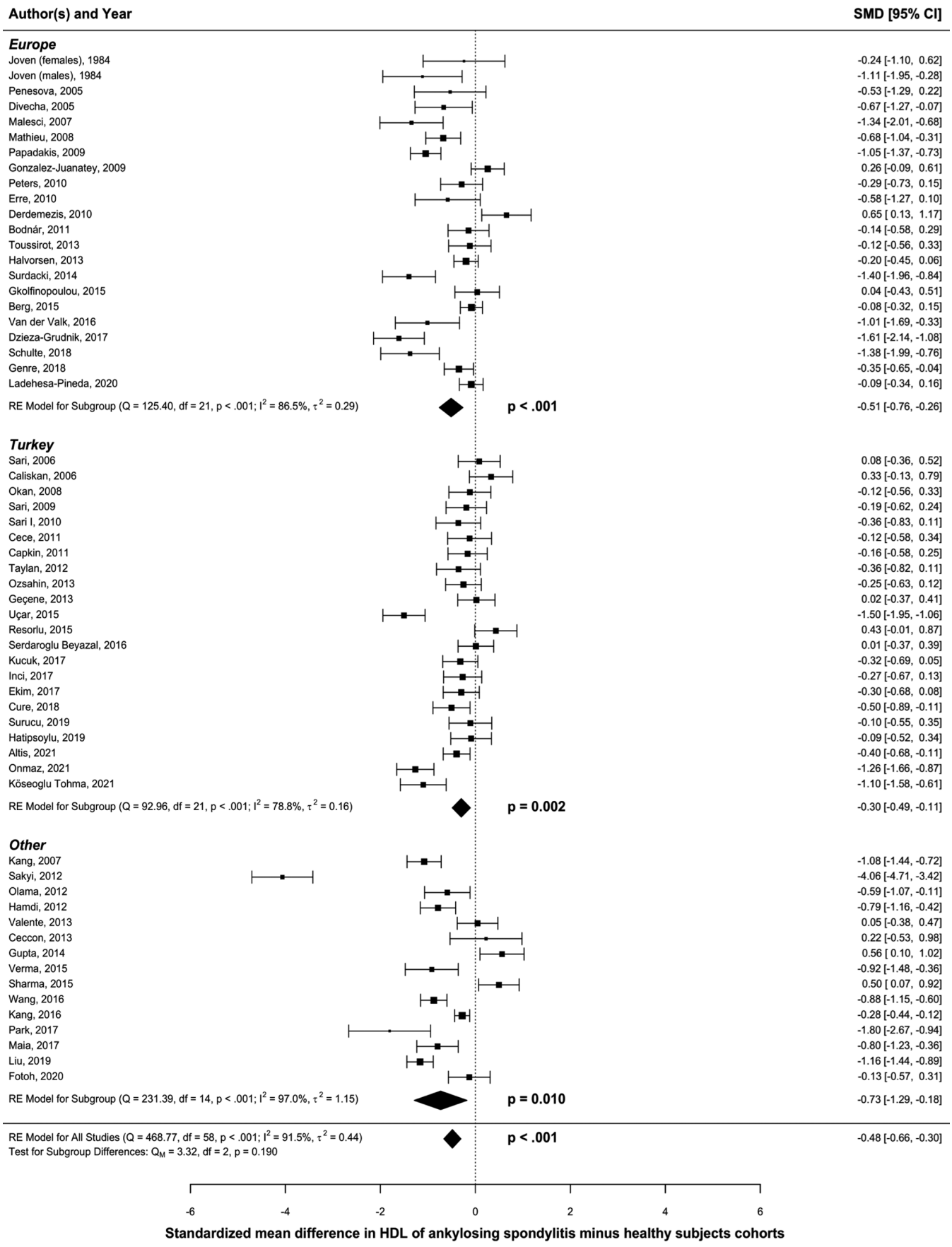

Fig. 4. Forest plot and subgroup analysis of HDL-C by Geographic Regions.

-0.42 (-0.56, -0.28). The funnel plot excluding the influential case (41), did not show asymmetry (Fig. 1) and Egger's test, commonly used to assess potential publication bias in a meta-analysis, is non-significant, p=0.068.

Forest plot of total cholesterol (TC) level standardised mean differences (SMDs) of AS minus HC were analysed by geographic regions (Fig. 2). The total unsegregated forest plot of 58 cohorts in all specified regions may be requested from the corresponding author. The 21 articles from Europe have a pooled Hedges' g of -0.29 (-0.53, -0.05), p=0.017. Pooled Hedges' g of 22 Turkish articles is -0.06 (-0.24, 0.13), p=0.543, and 13 articles from other specified regions is 0.00 (-0.36, 0.37), p=0.992. Geographic regions do not modify the pooled Hedges' g effect of AS on total cholesterol; the test for subgroup differences is non-significant (p=0.224), as shown in Figure 2.

The pooled Hedges' g (95% CI) of HDL-C in AS *versus* HC cohorts in 41 articles identified from database search is -0.61 (-0.84, -0.37), p<0.001, as compared to the 18 articles derived from references of -0.21 (-0.43, 0.00), p=0.050 (Fig. 3). The subgroups differ slightly (p=0.043), possibly due to a stronger AS *versus* HC differential in HDL-C in the larger database cohort, or the effect of the identified influential article by Sakyi SA *et al*., 2012.

Forest plot of the subgroup analysis of HDL-C by geographic regions (Fig. 4) shows significantly lower mean values for AS than HC subjects in each of the three regions with no significant subgroup difference (p=0.190). The mean SMD (95% CI) of 21 European articles is -0.51 (-0.76, -0.26), p<0.001, *versus* 22 Turkish articles having mean SMD of -0.30 (-0.49, -0.11), p=0.002, and 15 other articles having mean SMD of -0.73 (-0.66, -0.30), p=0.010 (Fig. 4). The forest plot of 59 unified HDL-C differences in AS minus HC subgroups is available on request from the corresponding author.

Moderator factors and indicators of inflammation, including ESR, CRP, and anti-TNF therapy in AS, were examined by meta-regression to investigate the significantly lower HDL-C levels in AS *versus* HC subjects (Table II). The AS minus HC difference in HDL-C was not related to meta-regression difference in CRP (p=0.37), ESR (p=0.13), or TNFi therapy (p=0.83) (Table II). The only significant (p<0.001) meta-regression was between triglycerides and CRP (Table II, Suppl. Fig. S2). The complimentary ESR difference in AS minus HC subjects and TG was non-significant (p=0.60) and had a positive regression slope (Table II).

Table II. Results of bubble plot meta-regressions of AS minus HC differences in inflammatory metrics and females (X-components) and lipids (Y-components).

AS minus HC lipid differences (Y-axis component)	AS minus HC differences in inflammatory metrics and percentage females (X-axis component)	Meta-regression Qm (df=1)	p-values	Slopes of regressions
Total cholesterol	CRP	1.30	0.25	-0.015
	ESR	2.32	0.13	0.020
	TNFi	0.32	0.57	-0.001
	Females	0.14	0.709	-0.003
Triglycerides	CRP	11.37	<.001	-0.033
	ESR	0.27	0.60	0.007
	TNFi	1.93	0.16	0.003
	Females	0.25	0.618	0.003
HDL cholesterol	CRP	0.80	0.37	0.011
	ESR	2.29	0.13	-0.029
	TNFi	0.04	0.83	0.001
	Females	2.74	0.10	-0.013
LDL cholesterol	CRP	1.73	0.19	-0.017
	ESR	2.10	0.15	0.030
	TNFi	0.00	0.99	0.000
	Females	0.31	0.577	0.004

The weighted mean (SD) ratio of total÷HDL cholesterol for AS (Panel A) is 3.95 (0.507), which is greater than the weighted mean (SD) for HC (Panel C) of 3.64 (0.458) (Fig. 5). The difference in AS minus HC weighted means (SDs) for the latter ratio is +0.31 (1.12), indicating a larger total÷HDL-C ratio in AS. These total÷HDL-C histogram panels (A, B, C) are reasonably symmetrical, except for HC (Panel C) having 8 values below the lowest value in AS of 2.90 (Panel A). The weighted mean (SD) ratio of $\log_{10}$(TG/HDL-C) in AS is 0.346 (0.558) (Panel B), which is larger than the HC values of 0.302 (0.558) (Panel D). Of note, 5 values in HC (Panel D) are below the lowest level in AS of -0.16 (Panel B). The AS minus HC difference in weighted means (SDs) of $\log_{10}$(TG/HDL-C) is 0.044 (0.138) (Panel F).

Discussion

A critical interpretation of results in this novel systematic review and meta-analysis of serum lipids in AS *versus* HC subjects indicates that HDL-C serum levels are significantly lower in AS, without meaningful difference in other lipids. A 2011 review of 13 reports on CVD mortality in AS and control cohorts found significantly decreased triglycerides, total cholesterol, and HDL-C in the AS subjects (5). The AS risk of CVD was suspected to be increased and attributed to either systemic inflammation or lower HDL-C levels (5). The current results therefore extend these findings to demonstrate that across a larger pool of studies, HDL-C levels are indeed lower in AS. Further, no significant relationship was found in this study between HDL-C serum levels and inflammatory indicators of ESR, CRP, and TNFi therapy. Funnel plot of SMD in HDL-C of AS minus HC subjects (Fig. 1) was symmetrical and did not indicate evidence of bias. The HDL-C serum levels were lower in AS *versus* HC subjects in both database and reference article sources (Fig. 3). No difference was found in the lower HDL-C levels of AS *versus* HC subjects by geographic regions (Fig. 4), suggesting that environmentally-determined dietary factors may not be a prominent influential factor.

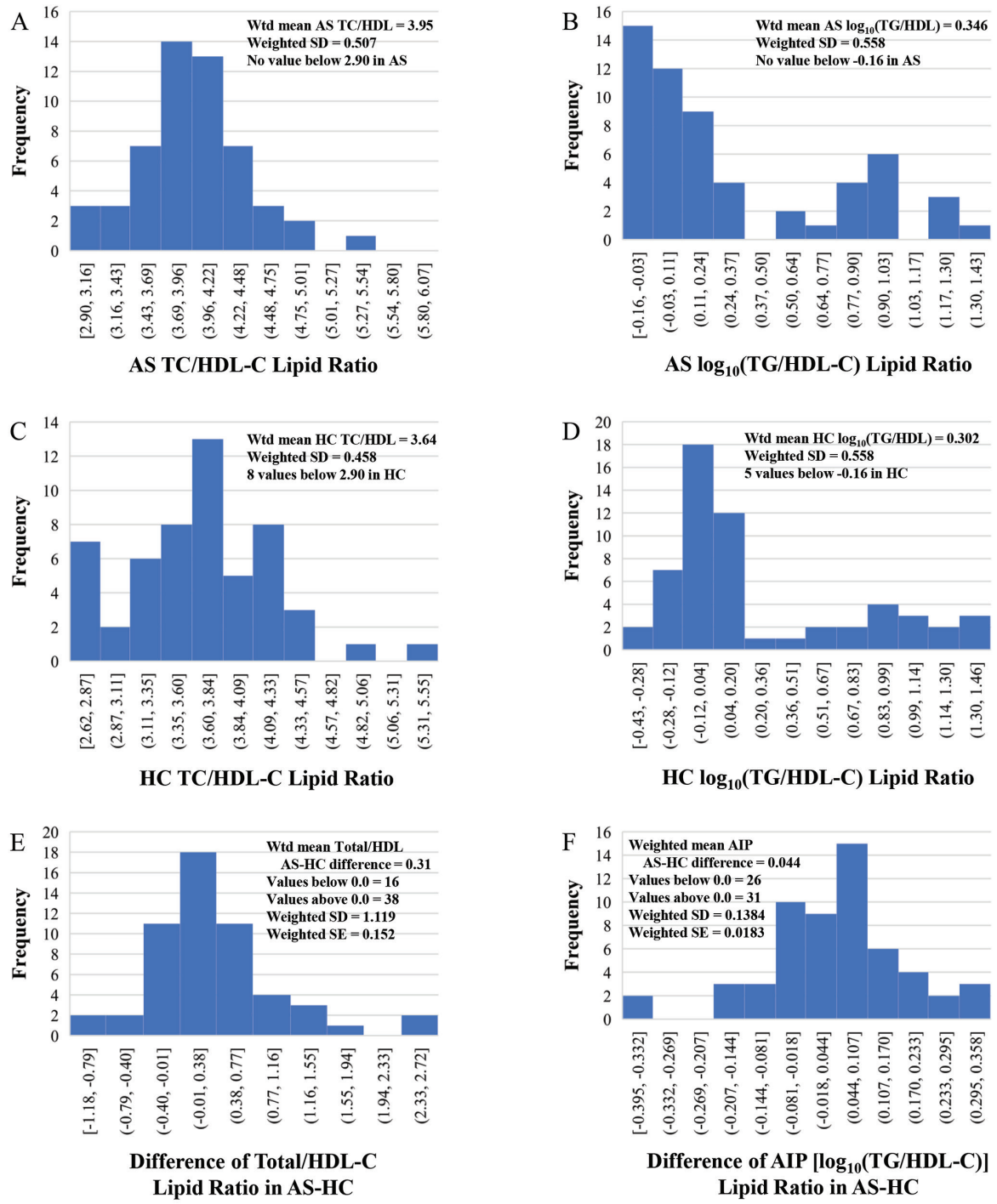

Fig. 5. Histograms of weighted means (SDs) of total C/HDL-C and log(TG/HDL-C) ratios in AS and HC subjects.

Lipid-related molecules share metabolic pathways, and it is difficult to distinguish the effect of one *versus* another in health and various diseases (6-8). The main structural difference between LDL-C and HDL-C particles is that the former has 25% protein whereas the latter has 50% protein. High-density lipoprotein cholesterol is the most complex class of heterogenous lipoproteins and its roles in diseases are poorly understood (6). The HDL-C is referred to as "good cholesterol" because higher levels are negatively associated with CVD, whereas LDL-C is referred to as "bad cholesterol" because of its positive CVD association (7, 8). Determinant factors for each lipid particle, like genetics, diet, physical capacity, body mass index (BMI), and insulin levels, have not been clearly differentiated or independently established (6).

Previous literature has shown several factors that can influence HDL-C levels in various populations, but not specifically AS. In an 8-year population-based longitudinal study of CVD risk factors in non-diabetic subjects, baseline fasting insulin was negatively correlated with HDL-C levels ($p<0.05$) after ad-

justment for age and BMI (88). Alcohol consumption was positively associated with HDL-C level in 5 population studies as a graded response even over low levels of consumption (89). Diet and increased physical activity resulted in decreased insulin resistance and increased HDL-C in control studies of overweight or obese persons (90). Exercise training alone for 3 months, without modification of dietary intake, increased HDL-C from mean (SD) 38 (10) to 41 (11) mg/dL (p<0.001) (91). In the latter study (91) of coronary population with mean age (SD) 61.2 (12.2) years, no significant lipid or insulin changes occurred. In AS or axSpA, it is not known if serum lipid profiles vary with cardiovascular risk (CVR) classification, as altered by the presence or absence of cIMT (92). Future studies are needed to determine if personal dietary lifestyle or long-duration physical activity limitations in AS are mainly responsible for the lower HDL-C serum levels than HC controls.

Systemic inflammatory mechanisms do not appear responsible for the significantly lower HDL-C levels in AS *versus* HC, as there were no significant effects of ESR, CRP, or TNFi therapy on HDL-C. The overall relation of inflammatory indicators in this study (Table II) do not seem to contribute to the significantly lower HDL-C levels in AS *versus* HC subjects.

A historical review of serum lipids in AS revealed a gradual conceptual evolution. Lower triglycerides and total cholesterol were reported in 8 AS males than population controls in 1978 (16). In 2010, serum lipids were reported associated with signs of accelerated preclinical atherosclerosis, including carotid intima media thickness (cIMT), in AS patients (33). In 2017, the LDL-C/HDL-C ratio and atherosclerosis was reported greater in AS than control patients and found correlated with cIMT (68). In 2018, atherogenic index of plasma was reported a useful marker in AS for subclinical atherosclerosis and was associated with cIMT (71). In 2021, HDL-C was reported significantly lower, and BMI significantly higher, in AS than non-radiographic axSpA patients (81). In a cohort of 60 AS and 60 HC subjects, arginine levels correlated positively with HDL-C and were significantly lower in 25 AS patients treated with TNFi therapy than the HC subjects (82). Age, disease duration, disease activity, inflammatory biomarkers, and obesity are being recognised as accelerating cIMT and other atherosclerosis indicators in AS patients (81-83, 92).

Ratios do not respond symmetrically to changes in the numerator and denominator and do not follow normal distributions, resulting in biased means, variance, or linear slopes, particularly in large-scale meta-analyses (85-87). Hence, we pursued weighted mean analyses to analyse the combined cohorts' ratio data. The ratio data for lipids indicate that there may be a difference between AS and HC in the total cholesterol÷HDL-C. We are unable to conclude if this difference is statistically significant due to the unknown variability around these ratios. Nevertheless, it is of interest and future studies should analyse these ratios between their AS and HC populations. If such difference were consistently found across studies, it would strengthen the significantly lower level of HDL-C in AS *versus* HC populations.

A limitation of this systematic review and meta-analysis is that all data are derived from cross-sectional, retrospective studies and none are longitudinal to know if significant relations persist over a meaningful duration. Also, no causal pathways can be suggested from the cross-sectional design. Bias could have operated without detection or resulted from incomplete retrieval of desired articles to test a valid relation of subject and outcome groups. Future studies could focus on early stage AS patients carefully matched to HC subjects and followed at least 5 years to determine if any significant initial correlations are influenced by onset age, disease duration, or moderator factors. Further analysis of moderator factors diminishing HDL-C levels promise to enhance the validity of the present findings and explain underlying mechanisms. The AS cohorts showed considerable variation by disease duration, age, gender, geographic origin, disease activity, and therapy. However, examination of these factors do not appear to have influenced the main results. The high heterogeneity of results in this meta-analysis limits the generalisation of the conclusions for a full spectrum of AS patients. Whether the observed lower levels of HDL-C in AS are resultant from physical activity limitations consequent to the disease, or its spinal structural alterations, is undetermined.

Our analysis has strengths including the extensive review and concordant results in subgroup analyses. The study design is favourable because most mediating variables in AS were matched in the selection of HC subjects in each cohort. Selection bias was not evident in full-text reviews, nor in funnel plot analysis. For HDL-C, after excluding the influential case (41, Sakyi SA *et al.*), the conclusion about significant difference between AS and control remained the same.

In summary, the main finding of this cross-sectional, retrospective systematic review and meta-analysis is the significantly lower mean HDL-C levels in AS *versus* HC subjects. Further, there appears to be a complementary increase in the ratio of total ÷ HDL-C serum levels. The lower HDL-C level in AS did not result from geographic areas, differences in percentage females in cohorts, nor inflammatory metrics of AS minus HC differences in ESR, CRP, or TNFi therapy. The strength of evidence was consistent for articles derived from database *versus* reference searches. These data indicate that HDL-C levels are lower in a large-scale, cross-sectional, heterogeneous cohort of AS subjects, and further investigation is warranted to determine the genesis of this alteration.

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References

1. BARALIAKOS X, VAN DER HEIJDE D, BRAUN J, LANDEWÉ RB: OMERACT magnetic resonance imaging initiative on structural and inflammatory lesions in ankylosing spondylitis--report of a special interest group at OMERACT 10 on sacroiliac joint and spine lesions. *J Rheumatol* 2011; 38(9): 2051-4. https://doi.org/10.3899/jrheum.110423
2. PAPAGORAS C, VOULGARI PV, DROSOS AA: Atherosclerosis and cardiovascular disease in the spondyloarthritides, particularly ankylosing spondylitis and psoriatic arthritis. *Clin Exp Rheumatol* 2013; 31(4): 612-20. PMID: 23406817.
3. LIEW JW, REVEILLE JD, CASTILLO M *et al*.: Cardiovascular risk scores in axial spondyloarthritis versus the general population: a cross-sectional study. *J Rheumatol* 2021; 48(3): 361-366. https://doi.org/10.3899/jrheum.200188
4. BIESBROEK PS, HESLINGA SC, VAN DE VEN PM *et al*.: Assessment of aortic stiffness in patients with ankylosing spondylitis using cardiovascular magnetic resonance. *Clin Rheumatol* 2018; 37(8): 2151-9. https://doi.org/10.1007/s10067-018-4135-x
5. MATHIEU S, GOSSEC L, DOUGADOS M, SOUBRIER M: Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis: *Arthritis Care Res* (Hoboken) 2011; 63(4): 557-63. https://doi.org/10.1002/acr.20364
6. SOLTANI S, SARAF-BANK S, BASIRAT R *et al*.: Community-based cardiovascular disease prevention programmes and cardiovascular risk factors: a systematic review and meta-analysis. *Public Health* 2021; 200: 59-70. https://doi.org/10.1016/j.puhe.2021.09.006.
7. CASTELLI WP, GARRISON RJ, WILSON PW, ABBOTT RD, KALOUSDIAN S, KANNEL WB: Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986; 256(20): 2835-8. https://doi.org/10.1001/jama.1986.03380200073024
8. KANNEL WB, WILSON PW: Efficacy of lipid profiles in prediction of coronary disease *Am Heart J* 1992; 124(3): 768-74. https://doi.org/10.1016/0002-8703(92)90288-7
9. DOBIASOVA M: Correspondence to: "atherogenic index of plasma and the risk of rapid progression of coronary atherosclerosis beyond traditional risk factors". *Atherosclerosis* 2021; 335: 148. https://doi.org/10.1016/j.atherosclerosis.2021.09.004
10. DAVIS CE, WILLIAMS DH, OGANOV RG *et al*.: Sex difference in high density lipoprotein cholesterol in six countries. *Am J Epidemiol* 1996; 143(11): 1100-6. https://doi.org/10.1093/oxfordjournals.aje.a008686
11. KIM JJ, YOON J, LEE YJ, PARK B, JUNG DH: Predictive value of the atherogenic index of plasma (AIP) for the risk of incident ischemic heart disease among non-diabetic Koreans. *Nutrients* 2021; 13(9): 3231. https://doi.org/10.3390/nu13093231
12. CURE E, ICLI A, USLU AU *et al*.: Atherogenic index of plasma: a useful marker for subclinical atherosclerosis in ankylosing spondylitis: AIP associate with cIMT in AS. *Clin Rheumatol* 2018; 37(5): 1273-80. https://doi.org/10.1007/s10067-018-4027-0
13. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG, PRISMA GROUP: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097
14. HOZO SP, DJULBEGOVIC B, HOZO I: Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5: 13. https://doi.org/10.1186/1471-2288-5-13
15. JAYEDI A, KHAN TA, AUNE D, EMADI A, SHAB-BIDAR S: Body fat and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Int J Obes* (Lond) 2022; 46(9): 1573-81. https://doi.org/10.1038/s41366-022-01165-5
16. RÖSSNER S: Further studies on serum lipoproteins in connective tissue diseases. *Atherosclerosis* 1978; 31(1): 93-9. https://doi.org/10.1016/0021-9150(78)90041-2
17. JOVEN J, RUBIÉS-PRAT J, RAS MR, DE LA FIGUERA M, LIENCE E, MASDEU S: High density lipoprotein cholesterol subfractions and apoprotein A-I in patients with rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum* 1984; 27(10): 1199-200. https://doi.org/10.1002/art.1780271021
18. DIVECHA H, SATTAR N, RUMLEY A, CHERRY L, LOWE GD, STURROCK R: Cardiovascular risk parameters in men with ankylosing spondylitis in comparison with non-inflammatory control subjects: relevance of systemic inflammation. *Clin Sci* (Lond) 2005; 109(2): 171-6. https://doi.org/10.1042/cs20040326
19. PENESOVA A, ROVENSKY J, ZLNAY M *et al*.: Attenuated insulin response and normal insulin sensitivity in lean patients with ankylosing spondylitis. *Int J Clin Pharmacol Res* 2005; 25(3): 107-14. PMID: 16366418.
20. CALISKAN M, ERDOGAN D, GULLU H *et al*.: Impaired coronary microvascular and left ventricular diastolic functions in patients with ankylosing spondylitis. *Atherosclerosis* 2008; 196(1): 306-12. https://doi.org/10.1016/j.atherosclerosis.2006.11.003
21. SARI I, OKAN T, AKAR S *et al*.: Impaired endothelial function in patients with ankylosing spondylitis. *Rheumatology* (Oxford) 2006; 45(3): 283-6. https://doi.org/10.1093/rheumatology/kei145
22. KANG E, CHOI S, LEE S, PARK Y: Atherogenic lipid profile in ankylosing spondylitis [abstract]. *Ann Rheum Dis* 2007; 66 (Suppl 2): 399-400.
23. MALESCI D, NIGLIO A, MENNILLO GA, BUONO R, VALENTINI G, LA MONTAGNA G: High prevalence of metabolic syndrome in patients with ankylosing spondylitis. *Clin Rheumatol* 2007; 26(5): 710-4. https://doi.org/10.1007/s10067-006-0380-5
24. SARI I, DEMIR T, KOZACI LD *et al*.: Body composition, insulin, and leptin levels in patients with ankylosing spondylitis. *Clin Rheumatol* 2007; 26(9): 1427-32. https://doi.org/10.1007/s10067-006-0509-6
25. MATHIEU S, JOLY H, BARON G *et al*.: Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. *Rheumatology* (Oxford) 2008; 47(8): 1203-7. https://doi.org/10.1093/rheumatology/ken198
26. OKAN T, SARI I, AKAR S *et al*.: Ventricular diastolic function of ankylosing spondylitis patients by using conventional pulsed wave Doppler, myocardial performance index and tissue Doppler imaging. *Echocardiography* 2008; 25(1): 47-56. https://doi.org/10.1111/j.1540-8175.2007.00541.x
27. GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MIRANDA-FILLOY JA *et al*.: The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. *Medicine* (Baltimore) 2009; 88(6): 358-65. https://doi.org/10.1097/md.0b013e3181c10773
28. PAPADAKIS JA, SIDIROPOULOS PI, KARVOUNARIS SA *et al*.: High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNF-alpha treatment: correlation with disease activity. *Clin Exp Rheumatol* 2009; 27(2): 292-8. PMID: 19473571.
29. SARI I, KEBAPCILAR L, ALACACIOGLU A *et al*.: Increased levels of asymmetric dimethylarginine (ADMA) in patients with ankylosing spondylitis. *Intern Med* 2009; 48(16): 1363-8. https://doi.org/10.2169/internalmedicine.48.2193
30. DERDEMEZIS CS, FILIPPATOS TD, VOULGARI PV, TSELEPIS AD, DROSOS AA, KIORTSIS DN: Leptin and adiponectin levels in patients with ankylosing spondylitis. The effect of infliximab treatment. *Clin Exp Rheumatol* 2010; 28(6): 880-3. PMID: 21122270.
31. ERRE GL, SANNA P, ZINELLU A *et al*.: Plasma asymmetric dimethylarginine (ADMA) levels and atherosclerotic disease in ankylosing spondylitis: a cross-sectional study. *Clin*

Rheumatol 2011; 30(1): 21-7. https://doi.org/10.1007/s10067-010-1589-x
32. KARKUCAK M, CAPKIN E, ALVER A *et al*.: The effect of anti-TNF agent on oxidation status in patients with ankylosing spondylitis. *Clin Rheumatol* 2010; 29(3): 303-7. https://doi.org/10.1007/s10067-009-1325-6
33. PETERS MJ, VAN EIJK IC, SMULDERS YM *et al*.: Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2010; 37(1): 161-6. https://doi.org/10.3899/jrheum.090667
34. SARI I, KEBAPCILAR L, TAYLAN A *et al*.: Fetuin-A and interleukin-18 levels in ankylosing spondylitis. *Int J Rheum Dis* 2010; 13(1): 75-81. https://doi.org/10.1111/j.1756-185x.2009.01448.x
35. BODNÁR N, KEREKES G, SERES I *et al*.: Assessment of subclinical vascular disease associated with ankylosing spondylitis. *J Rheumatol* 2011; 38(4): 723-9. https://doi.org/10.3899/jrheum.100668
36. CAPKIN E, KIRIS A, KARKUCAK M *et al*.: Investigation of effects of different treatment modalities on structural and functional vessel wall properties in patients with ankylosing spondylitis. *Joint Bone Spine* 2011; 78(4): 378-82. https://doi.org/10.1016/j.jbspin.2010.09.023
37. CECE H, YAZGAN P, KARAKAS E *et al*.: Carotid intima-media thickness and paraoxonase activity in patients with ankylosing spondylitis. *Clin Invest Med* 2011; 34(4): E225. https://doi.org/10.25011/cim.v34i4.15364
38. HAMDI W, CHELLI BOUAZIZ M, ZOUCH I *et al*.: Assessment of preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2012; 39(2): 322-6. https://doi.org/10.3899/jrheum.110792
39. KOCABAS H, KOCABAS V, BUYUKBAS S, MELIKOGLU MA, SEZER I, BUTUN B: The serum levels of resistin in ankylosing spondylitis patients: a pilot study. *Rheumatol Int* 2012; 32(3): 699-702. https://doi.org/10.1007/s00296-010-1651-7
40. OLAMA SM, ELARMAN MM: Evaluation of paraoxonase and arylesterase activities in Egyptian patients with ankylosing spondylitis. *Rheumatol Int* 2013; 33(6): 1487-94. https://doi.org/10.1007/s00296-012-2591-1
41. SAKYI SA, AGYEI-FREMPONG MT, QUANSAH RE: HLA-B27 and its associated clinical and biochemical presentation among Ghanaians with ankylosing spondylitis. *J Med Sci* 2012; 12(6): 161-67. https://doi.org/10.3923/jms.2012.161.167
42. CECCON FT, AZEVEDO VF, ENGELHORN CA *et al*.: Evaluation of sub-clinical atherosclerosis and plasma levels of minimally modified LDL in patients with ankylosing spondylitis and its correlation with disease activity. *Rev Bras Reumatol* 2013; 53(6): 470-5. https://doi.org/10.1016/j.rbr.2013.06.002
43. TAYLAN A, SARI I, KOZACI DL *et al*.: Evaluation of various endothelial biomarkers in ankylosing spondylitis. *Clin Rheumatol* 2012; 31(1): 23-8. https://doi.org/10.1007/s10067-011-1760-z
44. GEÇENE M, TUNCAY F, BORMAN P, YÜCEL D, SENES M, YILMAZ BK: Atherosclerosis in male patients with ankylosing spondylitis: the relation with methylenetetrahydrofolate reductase (C677T) gene polymorphism and plasma homocysteine levels. *Rheumatol Int* 2013; 33(6): 1519-24. https://doi.org/10.1007/s00296-012-2552-8
45. HALVORSEN S, VØLLESTAD NK, PROVAN SA *et al*.: Cardiorespiratory fitness and cardiovascular risk in patients with ankylosing spondylitis: a cross-sectional comparative study. *Arthritis Care Res* (Hoboken) 2013; 65(6): 969-76. https://doi.org/10.1002/acr.21926
46. OZSAHIN M, BUYUKKAYA R, BESIR FH *et al*.: Assessment of carotid intima-media thickness in ankylosing spondylitis patients. *Acta Med Mediterr* 2013; 29: 687-92.
47. SYNGLE A, VOHRA K, KHICHI D, GARG N, VERMA I, KAUR L: Spironolactone improves endothelial dysfunction in ankylosing spondylitis. *Clin Rheumatol* 2013; 32(7): 1029-36. https://doi.org/10.1007/s10067-013-2233-3
48. TOUSSIROT E, GRANDCLÉMENT E, GAUGLER B *et al*.: Serum adipokines and adipose tissue distribution in rheumatoid arthritis and ankylosing spondylitis. A comparative study. *Front Immunol* 2013; 4: 453. https://doi.org/10.3389/fimmu.2013.00453
49. VALENTE RL, VALENTE JM, DE CASTRO GR, ZIMMERMANN AF, FIALHO SC, PEREIRA IA: Subclinical atherosclerosis in ankylosing spondylitis: is there a role for inflammation? *Rev Bras Reumatol* 2013; 53(5): 377-81. https://doi.org/10.1590/S0482-50042013000500002
50. GUPTA N, SAIGAL R, GOYAL L, AGRAWAL A, BHARGAVA R, AGRAWAL A: Carotid intima media thickness as a marker of atherosclerosis in ankylosing spondylitis. *Int J Rheumatol* 2014; 2014: 839135. https://doi.org/10.1155/2014/839135
51. PAPAGORAS C, MARKATSELI TE, SAOUGOU I *et al*.: Cardiovascular risk profile in patients with spondyloarthritis. *Joint Bone Spine* 2014; 81(1): 57-63. https://doi.org/10.1016/j.jbspin.2013.03.019
52. SUNDSTRÖM B, JOHANSSON G, JOHANSSON I, WÅLLBERG-JONSSON S: Modifiable cardiovascular risk factors in patients with ankylosing spondylitis. *Clin Rheumatol* 2014; 33(1): 111-7. https://doi.org/10.1007/s10067-013-2410-4
53. SURDACKI A, SULICKA J, KORKOSZ M *et al*.: Blood monocyte heterogeneity and markers of endothelial activation in ankylosing spondylitis. *J Rheumatol* 2014; 41(3): 481-9. https://doi.org/10.3899/jrheum.130803
54. BERG IJ, VAN DER HEIJDE D, DAGFINRUD H *et al*.: Disease activity in ankylosing spondylitis and associations to markers of vascular pathology and traditional cardiovascular disease risk factors: a cross-sectional study. *J Rheumatol* 2015; 42(4): 645-53. https://doi.org/10.3899/jrheum.141018
55. GKOLFINOPOULOU C, STRATIKOS E, THEOFILATOS D *et al*.: Impaired antiatherogenic functions of high-density lipoprotein in patients with ankylosing spondylitis. *J Rheumatol* 2015; 42(9): 1652-60. https://doi.org/10.3899/jrheum.141532
56. RESORLU H, AKBAL A, RESORLU M *et al*.: Epicardial adipose tissue thickness in patients with ankylosing spondylitis. *Clin Rheumatol* 2015; 34(2): 295-9. https://doi.org/10.1007/s10067-014-2568-4
57. SHARMA SK, PRASAD KT, HANDA R, SHARMA SK: Increased prevalence of subclinical atherosclerosis in ankylosing spondylitis. *Indian J Rheumatol* 2015; 10(2): 53-57. https://doi.org/10.1016/j.injr.2015.02.002
58. UÇAR M, SARIKAYA S, SARP Ü *et al*.: Cardiometabolic risk factors in patients with ankylosing spondylitis. *Arch Rheumatol* 2015; 30(3): 221-25. https://doi.org/10.5606/ArchRheumatol.2015.5451
59. VERMA I, KRISHAN P, SYNGLE A: Predictors of atherosclerosis in ankylosing spondylitis. *Rheumatol Ther* 2015; 2(2): 173-82. https://doi.org/10.1007/s40744-015-0017-8
60. AVRAM C, DRĂGOI RG, POPOVICIU H, DRĂGOI M, AVRAM A, AMARICĂI E: Association between arterial stiffness, disease activity and functional impairment in ankylosing spondylitis patients: a cross-sectional study. *Clin Rheumatol* 2016; 35(8): 2017-22. https://doi.org/10.1007/s10067-016-3297-7
61. KANG KY, HER YH, JU JH, HONG YS, PARK SH: Radiographic progression is associated with increased cardiovascular risk in patients with axial spondyloarthritis. *Mod Rheumatol* 2016; 26(4): 601-6. https://doi.org/10.3109/14397595.2015.1119348
62. SERDAROĞLU BEYAZAL M, ERDOĞAN T, TÜRKYILMAZ AK *et al*.: Relationship of serum osteoprotegerin with arterial stiffness, preclinical atherosclerosis, and disease activity in patients with ankylosing spondylitis. *Clin Rheumatol* 2016; 35(9): 2235-41. https://doi.org/10.1007/s10067-016-3198-9
63. VAN DER VALK FM, BERNELOT MOENS SJ, VERWEIJ SL *et al*.: Increased arterial wall inflammation in patients with ankylosing spondylitis is reduced by statin therapy. *Ann Rheum Dis* 2016; 75(10): 1848-51. https://doi.org/10.1136/annrheumdis-2016-209176
64. WANG HH, WANG QF: Low vaspin levels are related to endothelial dysfunction in patients with ankylosing spondylitis. *Braz J Med Biol Res* 2016; 49(7): e5231. https://doi.org/10.1590/1414-431X20165231
65. DZIEŻA-GRUDNIK A, SULICKA J, STRACH M *et al*.: Arterial stiffness is not increased in patients with short duration rheumatoid arthritis and ankylosing spondylitis. *Blood Press* 2017; 26(2): 115-21. https://doi.org/10.1080/08037051.2016.1232586
66. EKIM AA, GÖNÜLLÜ E, HAMARAT H, KAYA DS, YURDASIPER A, MUSMUL A: Subclinical carotid atherosclerosis and vitamin D in patients with ankylosing spondylitis. *J Clin Anal Med* 2017; 8(4): 261-6. https://doi.org/10.4328/jcam.4840
67. INCI U, YILDIZ A, BATMAZ I, TEKBAS E: Assessment of serum asymmetric dimethylarginine levels and left ventricular diastolic function in patients with ankylosing spondylitis. *Int J Rheum Dis* 2017; 20(2): 238-44. https://doi.org/10.1111/1756-185x.12608
68. KUCUK A, UĞUR USLU A, ICLI A *et al*.: The LDL/HDL ratio and atherosclerosis in ankylosing spondylitis. *Z Rheumatol* 2017; 76(1): 58-63. https://doi.org/10.1007/s00393-016-0092-4
69. MAIA DG, AUGUSTO KL, BEZERRA MC,

RODRIGUES CEM: Metabolic syndrome in patients with ankylosing spondylitis receiving anti-TNFα therapy: association with predictors of cardiovascular risk. *Clin Rheumatol* 2017; 36(10): 2371-76. https://doi.org/10.1007/s10067-017-3623-8
70. PARK JH, LEE SG, JEON YK, PARK EK, SUH YS, KIM HO: Relationship between serum adipokine levels and radiographic progression in patients with ankylosing spondylitis: a preliminary 2-year longitudinal study. *Medicine* (Baltimore) 2017; 96(33): e7854. https://doi.org/10.1097/md.0000000000007854
71. CURE E, ICLI A, USLU AU *et al*.: Atherogenic index of plasma: a useful marker for subclinical atherosclerosis in ankylosing spondylitis: AIP associate with cIMT in AS. *Clin Rheumatol* 2018; 37(5): 1273-80. https://doi.org/10.1007/s10067-018-4027-0
72. GENRE F, RUEDA-GOTOR J, REMUZGO-MARTÍNEZ S *et al*.: Association of circulating calprotectin with lipid profile in axial spondyloarthritis. *Sci Rep* 2018; 8(1): 13728. https://doi.org/10.1038/s41598-018-32199-3
73. SCHULTE DM, PAULSEN K, TÜRK K *et al*.: Small dense LDL cholesterol in human subjects with different chronic inflammatory diseases. *Nutr Metab Cardiovasc Dis* 2018; 28(11): 1100-05. https://doi.org/10.1016/j.numecd.2018.06.022
74. ZARDI EM, PIPITA ME, GIORGI C, LICHINCHI D, ZARDI DM, AFELTRA A: Differences in carotid atherosclerosis between patients with ankylosing spondylitis treated with tumor necrosis factor-α antagonists and healthy matched controls. *Medicine* (Baltimore) 2018; 97(27): e11250. https://doi.org/10.1097/md.0000000000011250
75. HATIPSOYLU E, ŞENGÜL İ, KAYA T *et al*.: Assessment of subclinical atherosclerotic cardiovascular disease in patients with ankylosing spondylitis. *Anatol J Cardiol* 2019; 22(4): 185-91. https://doi.org/10.14744/AnatolJCardiol.2019.13367
76. LIU M, HUANG Y, HUANG Z *et al*.: Prevalence of metabolic syndrome and its associated factors in Chinese patients with ankylosing spondylitis. *Diabetes Metab Syndr Obes* 2019; 12(4): 477-84. https://doi.org/10.2147/dmso.S197745
77. SURUCU GD, YILDIRIM A, YETISGIN A, AKTURK E: Epicardial adipose tissue thickness as a new risk factor for atherosclerosis in patients with ankylosing spondylitis. *J Back Musculoskelet Rehabil* 2019; 32(2): 237-43. https://doi.org/10.3233/bmr-160650
78. FOTOH DS, SERAG DM, BADR IT, SAIF DS: Prevalence of subclinical carotid atherosclerosis and vitamin D deficiency in Egyptian ankylosing spondylitis patients. *Arch Rheumatol* 2020; 35(3): 335-42. https://doi.org/10.46497/ArchRheumatol.2020.7694
79. LADEHESA-PINEDA ML, ARIAS DE LA ROSA I, LÓPEZ MEDINA C *et al*.: Assessment of the relationship between estimated cardiovascular risk and structural damage in patients with axial spondyloarthritis. *Ther Adv Musculoskelet Dis* 2020; 12. https://doi.org/10.1177/1759720X20982837
80. SARP Ü, ÜSTÜNER E, KUTLAY S, ATAMAN Ş, KUTLAY S: Biomarkers of cardiovascular disease in patients with ankylosing spondylitis. *Arch Rheumatol* 2020; 35(3): 435-39. https://doi.org/10.46497/ArchRheumatol.2020.7868
81. KÖSEOĞLU TOHMA E, GÜNENDI Z, ÖZYEMIŞÇI TAŞKIRAN Ö, MENGI G, DEMIRSOY N, TAŞ N: Exercise capacity in axial spondyloarthritis and associated factors: A cross-sectional controlled study. *Int J Rheum Dis* 2021; 24(8): 1014-23. https://doi.org/10.1111/1756-185x.14155
82. ONMAZ DE, ISIK K, SIVRIKAYA A *et al*.: Determination of serum methylarginine levels by tandem mass spectrometric method in patients with ankylosing spondylitis. *Amino Acids* 2021; 53(9): 1329-38. https://doi.org/10.1007/s00726-021-03046-z
83. ALTAS A, YILMAZ S, AYHAN TL, NAS K: Evaluation of cardiometabolic risk factors in patients with ankylosing spondylitis [abstract]. *Clin Exp Rheumatol* 2021; 39(5): 1257.
84. CHEN Y, CHANG Z, LIU Y *et al*.: Triglyceride to high-density lipoprotein cholesterol ratio and cardiovascular events in the general population: A systematic review and meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis* 2022; 32(2): 318-29. https://doi.org/10.1016/j.numecd.2021.11.005
85. SENN S: The variance of the ratio of two random variables. *Centre de Recherche Public* 2012. http://www.senns.uk/Stats_Notes/Variance_of_a_ratio.pdf
86. ISLES PDF: The misuse of ratios in ecological stoichiometry. *Ecology* 2020; 101(11): e03153. https://doi.org/10.1002/ecy.3153
87. LAJEUNESSE MJ: Bias and correction for the log response ratio in ecological meta-analysis. *Ecology* 2015; 96(8): 2056-63. https://doi.org/10.1890/14-2402.1
88. MITCHELL BD, HAFFNER SM, HAZUDA HP, VALDEZ R, STERN MP: The relation between serum insulin levels and 8-year changes in lipid, lipoprotein, and blood pressure levels. *Am J Epidemiol* 1992; 136(1): 12-22. https://doi.org/10.1093/oxfordjournals.aje.a116416
89. CASTELLI WP, DOYLE JT, GORDON T *et al*.: Alcohol and blood lipids. The cooperative lipoprotein phenotyping study. *Lancet* 1977; 2(8030): 153-5. https://doi.org/10.1016/s0140-6736(77)90176-3
90. SALAS-SALVADÓ J, DÍAZ-LÓPEZ A, RUIZ-CANELA M *et al*.: Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. *Diabetes Care* 2019; 42(5): 777-788. https://doi.org/10.2337/dc18-0836
91. BROCHU M, POEHLMAN ET, SAVAGE P, FRAGNOLI-MUNN K, ROSS S, ADES PA: Modest effects of exercise training alone on coronary risk factors and body composition in coronary patients. *J Cardiopulm Rehabil* 2000; 20(3): 180-8. https://doi.org/10.1097/00008483-200005000-00006
92. RUEDA-GOTOR J, QUEVEDO-ABELEDO JC, CORRALES A *et al*.: Reclassification into very-high cardiovascular risk after carotid ultrasound in patients with axial spondyloarthritis. *Clin Exp Rheumatol* 2020; 38(4): 724-31. PMID: 32083538.