Cholesterol, lipoproteins and subclinical interstitial lung disease: the MESA study

Abstract

We investigated associations of plasma lipoproteins with subclinical interstitial lung disease (ILD) by measuring high attenuation areas (HAA: lung voxels between −600 and −250 Hounsfield units) in 6700 adults and serum MMP-7 and SP-A in 1216 adults age 45–84 without clinical cardiovascular disease in Multi-Ethnic Study of Atherosclerosis. In cross-sectional analyses, each SD decrement in high density lipoprotein cholesterol (HDL-C) was associated with a 2.12% HAA increment (95% CI 1.44% to 2.79%), a 3.53% MMP-7 increment (95% CI 0.93% to 6.07%) and a 6.37% SP-A increment (95% CI 1.35% to 11.13%), independent of demographics, smoking and inflammatory biomarkers. These findings support a novel hypothesis that HDL-C might influence subclinical lung injury and extracellular matrix remodelling.

Cardiovascular disease (CVD) is a prevalent comorbidity in adults with fibrotic interstitial lung disease (ILD), yet the mechanisms underlying this association remain unclear.[1–3] Lipids and lipoproteins contribute to the pathogenesis of CVD and in recent years have been linked to a number of lung diseases, including asthma and COPD.[4 5] However, few studies have looked at the role of lipids and lipoproteins in interstitial lung injury, inflammation and fibrosis.[6 7]

Imaging-based identification of lung injury, matrix remodelling and fibrosis in asymptomatic individuals is a novel way of studying subclinical ILD and may lead to a better understanding of the early causes of fibrosis. Two methods have been developed and validated to identify subclinical ILD: automated detection using quantitative CT densitometry to measure increased lung attenuation (high attenuation areas, HAA) and visual inspection for the presence of interstitial lung abnormalities (ILA).[8–11] In the current study, we examined associations of plasma lipids and lipoproteins with HAA, ILA and serum biomarkers of lung inflammation and extracellular matrix remodelling (SP-A and MMP-7) in the Multi-Ethnic Study of Atherosclerosis (MESA).[12–15] We hypothesised that the presence of coronary artery calcium, high low density lipoprotein cholesterol (LDL-C), low high density lipoprotein cholesterol (HDL-C) and their respective components would be associated with HAA, ILA and higher MMP-7/SP-A levels independent of demographic characteristics, smoking and inflammatory biomarkers.

Full Methods are available in the online supplementary data.

The MESA is a multicentre, prospective cohort study of 6814 adults age 45–84 sponsored by the National Heart Lung and Blood Institute to investigate the progression of subclinical CVD. The participant selection criteria have been previously described.[16] Notably, there were no selection criteria based on lung disease, respiratory symptoms or smoking history. MESA was approved by institutional review boards at all collaborating centres, and all participants provided written informed consent for participation.

Lung attenuation was measured on cardiac CT scans performed at baseline. Quantitative image attenuation was measured using a modified version of the Pulmonary Analysis Software Suite at a single reading centre by trained readers. HAA was defined as the volume of imaged lung having CT attenuation values between −600 and −250 Hounsfield units.[8 9] ILA was visually assessed on full lung CT scans, as previously described.[9–11]

Of the 6814 MESA participants, there were 6700 with available lipid measurements included in HAA analyses, 2391 in ILA analyses and 1216 in MMP-7 and SP-A analyses, with sampling frame previously described.[9] The median (IQR) HAA was 4.2% (3.5%–5.4%) of total imaged lung.

In multivariable-adjusted models, there was a significant association between the presence of coronary artery calcium, HAA and ILA. The presence of coronary artery calcium was associated with 1.47% increment in HAA (95% CI 0.19 to 2.77) and with a 57% greater odds of ILA (OR 1.58, 95% CI 1.18 to 2.08). Greater total cholesterol, HDL-C, LDL-C and triglyceride levels were each associated with lower HAA (table 1). However, the associations of both LDL-C and triglycerides with HAA were greatly attenuated by further adjustment for left ventricular function. On the other hand, the association between greater HDL-C and lower HAA was only marginally changed and remained significant (figure 1). This association also persisted across HDL particle size and for ApoA-1, the major protein component of HDL.

In a multivariable-adjusted model, there were no associations of baseline HDL-C, LDL-C, triglycerides, ApoA-1, ApoB, presence of diabetes mellitus, hypertension or statin use with the presence of ILA assessed at 10-year follow-up. In a multivariable-adjusted model (table 2), each SD decrement in HDL-C was associated with a 3.53% increment in MMP-7 (95% CI 0.93% to 6.07%) and a 6.37% increment in SP-A (95% CI 1.35% to 11.13%).

Additional analyses are presented in online supplementary tables S1–S9 and figures S1–S2.

In this large cohort of community-dwelling adults, the presence of coronary artery calcium was associated with two measures of subclinical ILD (HAA and ILA), providing further support for a link between CVD and ILD.[1–3] We also found that lower plasma HDL-C and ApoA-1 were each associated with greater HAA and greater serum MMP-7 and SP-A levels, independent of smoking, demographic factors, inflammatory biomarkers and measures of left ventricular function, a finding consistent with a previous study

Table 1 Associations of cholesterol and lipoproteins with high attenuation area (HAA)

	% change in HAA (95% CI)*	p Value
Total cholesterol	−1.32 (−1.89 to −0.75)	<0.001
HDL-C, mg/dL	−2.12 (−2.79 to −1.44)	<0.001
LDL-C, mg/dL	−0.84 (−1.41 to −0.28)	0.004
Triglycerides	−0.82 (−1.45 to −0.18)	0.01
Large HDL, 9.4–14 nm	−1.10 (−1.93 to −0.26)	0.01
Medium HDL, 8.2–9.4 nm	−2.56 (−3.31 to −1.80)	<0.001
Small HDL, 7.3–8.2 nm	−2.69 (−3.44 to −1.94)	<0.001
Large LDL, 20.5–23 nm	−1.36 (−2.06 to −0.66)	<0.001
Small LDL, 18–20.5 nm	−0.73 (−1.56 to 0.11)	0.09
Apolipoprotein A-1	−1.66 (−2.36 to −0.97)	<0.001
Apolipoprotein B	−0.69 (−1.37 to −0.01)	0.048

Solid lines separate distinct models. Each model includes all exposure variables listed and is additionally adjusted for age, gender, race/ethnicity, educational attainment, height, body mass index, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, diuretic use, statin use, presence of hypertension, presence of diabetes mellitus, coronary artery calcium, study site, milliampere dose, total volume imaged lung, per cent emphysema on CT, interleukin-6 and C reactive protein.
*Reported per SD in each exposure variable.

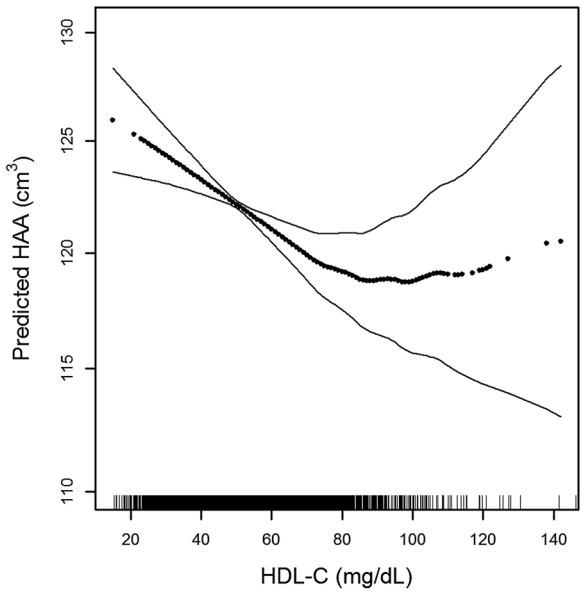

Figure 1 Continuous association between HDL-C and high attenuation areas (HAA) adjusted for age, gender, race/ethnicity, educational attainment, height, body mass index, waist circumference, smoking status, cigarette pack-years, presence of hypertension, presence of diabetes, low-density lipoprotein, triglycerides, C reactive protein, interleukin 6, glomerular filtration rate, statin use, diuretic use, coronary artery calcium, study site, milliampere dose, total volume imaged lung, per cent emphysema on CT, left ventricular ejection fraction and left ventricular end-diastolic mass; p for non-linearity 0.009, p for association <0.001. Dark dotted line is the continuous association. Thin solid lines are the 95% confidence bands. Each point in the graph and each vertical hashmark in the rug plot along the x axis represent one study participant.

Table 2 Associations of cholesterol and lipoproteins with MMP-7 and SP-A

	% change in MMP-7 (95% CI)*	p Value	% change in SP-A (95% CI)*	p Value
Total cholesterol	−0.01 (−2.25 to 2.28)	0.99	1.43 (−2.95 to 6.00)	0.52
HDL-C, mg/dL	−3.53 (−6.07 to −0.93)	0.008	−6.37 (−11.13 to −1.35)	0.01
LDL-C, mg/dL	0.35 (−2.55 to 1.89)	0.76	3.44 (−0.98 to 8.05)	0.13
Triglycerides	2.81 (0.30 to 5.37)	0.03	−3.11 (−7.69 to 1.70)	0.20
Large HDL, 9.4–14 nm	−4.10 (−7.26 to −0.84)	0.01	−14.39 (−19.82 to −8.59)	<0.001
Medium HDL, 8.2–9.4 nm	−4.92 (−7.61 to −2.14)	<0.001	−1.67 (−7.06 to 4.02)	0.56
Small HDL, 7.3–8.2 nm	−5.32 (−8.03 to −2.53)	<0.001	−8.23 (−13.31 to −2.86)	0.003
Large LDL, 20.5–23 nm	−4.86 (−7.50 to −2.15)	<0.001	−0.68 (−6.02 to 4.96)	0.81
Small LDL, 18–20.5 nm	−1.51 (−4.73 to 1.81)	0.37	−7.35 (−13.18 to −1.12)	0.02
Apolipoprotein A-1	−2.83 (−5.32 to −0.27)	0.03	−4.79 (−9.56 to 0.12)	0.06
Apolipoprotein B	1.74 (−0.64 to 4.18)	0.15	1.51 (−3.06 to 6.36)	0.52

Solid lines separate distinct models. Each model includes all exposure variables listed and is additionally adjusted for age, gender, race/ethnicity, body mass index, smoking status, cigarette pack-years, presence of coronary artery calcium, statin use, interleukin 6 and C reactive protein.
*Reported per SD in each exposure variable.

that found lower HDL-C levels in 39 adults with pulmonary fibrosis compared with healthy controls.[6] Our findings suggest a novel hypothesis that HDL-C levels or its components might exert protective effects in subclinical ILD. Candidate mechanisms by which HDL-C might attenuate subclinical lung inflammation, extracellular matrix remodelling and fibrosis include modulation of endothelial function, protection against inflammation and oxidative stress, and alterations in surfactant function.[17–19] ApoA-I has previously been shown to have beneficial effects in reducing lung inflammation and fibrosis in animal models,[7] and greater small and medium-size HDL particle concentrations are associated with increased non-cardiovascular, non-cancer chronic inflammation-related deaths in MESA,[20] supporting an anti-inflammatory role of small HDL particles in the lungs.

There are several limitations to our study, including the potential for residual confounding, the possibility that HAA likely includes pulmonary oedema, the lack of pathological validation of HAA and the use of cardiac rather than full lung CT scans to measure HAA. In addition, we found that HDL-C was not associated with ILA. This lack of consistency may reflect the 10-year latency period between baseline measurements of lipids and ILA, or it may reflect different stages of disease identified by the two measures of subclinical ILD. Furthermore, the clinical significance of elevated HAA, MMP-7 and SP-A in asymptomatic individuals is uncertain, limiting inferences about the role of HDL-C in fibrotic lung disease.

In summary, we found novel associations of greater HDL-C and ApoA-1 levels with lower HAA, a quantitative CT measure of subclinical lung inflammation and extracellular matrix remodelling, and with biomarkers of lung injury and extracellular matrix remodelling. This finding remains unexplained, but suggests a protective role of lipoproteins in ILD pathogenesis. More work is needed now to elucidate the mechanisms linking these two conditions, and the role that low lipoprotein levels might play in the pathogenesis of ILD.

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