ORIGINAL RESEARCH

Hepatosteatosis and atherosclerotic plaque on coronary computed tomography angiography

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Disclosures

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Hepatosteatosis and Atherosclerotic Plaque on Coronary CT Angiography

Key Points

Hepatosteatosis was common, occurring in 9% undergoing CT coronary angiography.

Participants with hepatosteatosis had more coronary artery disease on CT, including a higher coronary artery calcium score (43 Agatston units [AU] versus 19 AU, *P* = .046).

Hepatosteatosis was associated with a higher low-attenuation plaque burden (5.11% versus 4.07%, *P* = .04), but was not an independent predictor when adjusted for cardiovascular risk score (exp(β), 1.13 [95% CI: 0.57, 2.24]; *P* = .72).

Summary Statement

Hepatosteatosis was associated with coronary artery disease on CT, including an increased burden of low attenuation plaque, but this was not independent of other cardiovascular risk factors.

Abbreviations

AU = Agatston units

CCTA = CT coronary angiography

HU = Hounsfield units

NAFLD = non-alcoholic fatty liver disease

SCOT-HEART = Scottish Computed Tomography of the HEART

Abstract

Purpose

To assess the association between non-alcoholic fatty liver disease (NAFLD) and quantitative atherosclerotic plaque on CT.

Materials and Methods

In this post-hoc analysis of the prospective Scottish Computed Tomography of the HEART trial (November 2010 to September 2014), hepatosteatosis and coronary artery calcium score were measured on non-contrast CT. Presence of stenoses, visually assessed high-risk plaque, and quantitative plaque burden were assessed on coronary CT angiography. Multivariable models were constructed to assess the impact of hepatosteatosis and cardiovascular risk factors on coronary artery disease.

Results

Images from 1726 participants (mean age, 58 years ± 9 [standard deviation]; 974 men) were included. Participants with hepatosteatosis (n=155/1726, 9%) had a higher BMI, more hypertension and diabetes mellitus, and higher cardiovascular risk scores (P < .001 for all) compared with those without hepatosteatosis. They had increased coronary artery calcium scores (median, 43 [interquartile range, 0 to 273] Agatston units [AU] versus 19 [0 to 225] AU, P = .046), more non-obstructive disease (48% versus 37%, P = .02) and higher low-attenuation plaque burden (5.11% [0 to 7.16] versus 4.07% [0 to 6.84], P = .04). However, these associations were not independent of cardiovascular risk factors. Over median 4.7 years, there was no evidence of a

difference in myocardial infarction between those with and without hepatosteatosis (1.9% versus 2.4%, *P* = .92).

Conclusion

Hepatosteatosis on CT was associated with an increased prevalence of coronary artery disease on CT, but this was not independent of the presence of cardiovascular risk factors.

ClinicalTrials.gov: NCT01149590

Key words

Coronary artery disease, nonalcoholic fatty liver disease, hepatosteatosis, computed tomography, plaque quantification.

Introduction

Non-alcoholic fatty liver disease (NAFLD) reflects a spectrum of liver diseases characterized by the deposition of fat within hepatocytes, with histological findings progressively showing steatosis, hepatitis, fibrosis and cirrhosis. It is the commonest cause of chronic liver disease, with a growing global prevalence and is predicted to affect up to 33% of adults in the US by 2030.(1)

The etiology of NAFLD is unknown, but there is overlap between the presence of NAFLD and obesity, insulin resistance and all components of metabolic syndrome. Importantly, the primary cause of mortality in patients with NAFLD is cardiovascular disease (1). NAFLD is associated with increased arterial stiffness, carotid intima-media thickness and coronary microvascular dysfunction (2, 3). Hepatosteatosis, the progressive fat deposition in the liver which characterizes NAFLD, can be identified on CT by a reduction in liver attenuation or a change in the ratio of liver to splenic attenuation (4, 5).

The presence of coronary artery calcification on CT is a marker of coronary artery disease and is a robust predictor of subsequent cardiac events in symptomatic and asymptomatic patients. Furthermore, management based on coronary CT angiography (CCTA) can improve outcomes in symptomatic patients presenting to cardiology outpatient clinics (6). CCTA can also provide information on the presence of visually assessed high-risk plaques which may be associated with subsequent events (7). More recently, quantitative assessment of atherosclerotic plaque burden has enabled robust quantification of coronary plaque characteristics across the

coronary tree, with the ability to predict patients at risk of myocardial infraction and culprit lesions in future acute coronary syndromes (8).

The overlap between hepatosteatosis and coronary artery disease is currently uncertain. The presence of hepatosteatosis on CT is associated with an increase in the presence, severity and progression of coronary artery calcification (2, 9-11) and coronary artery stenoses (12, 13). In addition, patients with hepatosteatosis have an increased prevalence of visually assessed high-risk plaques (14, 15) and more non-calcified plaque (16). However, the association between hepatosteatosis and quantitative atherosclerotic plaque burden assessments has not previously been well-established in the literature.

In this study, we aimed to determine whether hepatosteatosis on CT is associated with an increased burden of high-risk coronary atherosclerotic plaque and explore whether any potential associations were independent of established cardiovascular risk factors.

Materials and Methods

Study Design

This was a post-hoc analysis of CT scans performed as part of the Scottish Computed Tomography of the HEART (SCOT-HEART) trial (ClinicalTrials.gov: NCT01149590) (17). SCOT-HEART is a multicenter randomized controlled trial assessing the use of CCTA in patients attending cardiology outpatient clinics with suspected angina due to coronary heart disease. The primary results have been published previously (6, 18, 19). The study was performed with approval from the local ethics committee and all participants provided written informed consent.

Study Participants

Participants who underwent CT as part of SCOT-HEART where part of the liver was visualized in the field-of-view (greater than 4 slices) were included. Inclusion criteria for SCOT-HEART were age 18 to 75 years and referral to out-patient cardiology chest pain clinics. Exclusion criteria were inability to undergo CT, renal failure (serum creatinine >250 μmol/L or estimated glomerular filtration rate <30 mL/min/1.73 m^2), allergy to iodine-based contrast media, inability to give informed consent, known pregnancy, and acute coronary syndrome within previous 3 months. Importantly, patients were not excluded based on body mass index (BMI) or coronary artery calcium score. Information on cardiovascular risk factors was obtained from the SCOT-HEART database. Cardiovascular risk was assessed using the ASSIGN (ASsessing cardiovascular risk using SIGN guidelines) cardiovascular risk score, which has been validated and calibrated in our Scottish population (20). The ASSIGN score includes age, sex, family history of coronary heart disease or stroke, social

deprivation, diabetes, rheumatoid arthritis, smoking, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol and provides a 10-year cardiovascular risk score.

CT Acquisition

Participants underwent non-contrast electrocardiogram-gated CT for coronary calcium scoring and contrast-enhanced CCTA, as described previously (17). CT was performed using 64-multidetector (Brilliance 64, Philips Medical Systems, Netherlands and Biograph mCT, Siemens, Germany) or 320-multidetector (Aquilion ONE, Toshiba Medical Systems, Japan) scanners. CCTA was performed during suspended respiration with electrocardiogram gating and tube voltage (100 or 120 kV), current and volume of iodine-based contrast adjusted based on BMI. Rate limiting medication was administered for participants with a heart rate above 65 beats per minute and sublingual glyceryl trinitrate was administered unless contraindicated.

Assessment of the Liver on CT

Liver attenuation was measured using imaging software (OsiriX DICOM Viewer, V11, Geneva, Switzerland) blind to clinical information, other CT findings, and outcomes (MW radiologist >10 years of experience, JS in training). The liver was identified on non-contrast CT, and a circular region of interest (mean 2.4 ± 0.89 [standard deviation] cm^2) was drawn on axial images within the liver parenchyma, distant from vascular structures. Mean attenuation within the region of interest was recorded. An attenuation of less than 40 Hounsfield units (HU) was used to identify participants with hepatosteatosis on CT (5). This threshold has been shown to correlate well with pathological liver fat content on resected liver specimens (21). To assess inter- and

intra-rater reliability, a random sample of 50 CT scans was assessed twice by one observer, and by a second observer, both blinded to other findings.

Assessment of Coronary Artery Disease on CT

Information on coronary artery disease on CT was obtained from the SCOT-HEART database. Coronary artery calcium scoring was performed using the Agatston method on non-contrast CT. Coronary artery stenoses on CCTA were identified on a per-segment basis using a 15-segment model. CCTA scans were then classified as normal, non-obstructive (one or more lesion <70% or <50% in left main stem), or obstructive (one or more lesion ≥70% or ≥50% in left main stem). Visual assessment of adverse plaques was performed on a per-segment basis to identify positive remodeling, low-attenuation plaque, spotty calcification and the “napkin ring” sign, as previously described (7). An adverse plaque was defined as having positive remodeling or low-attenuation plaque, and assessed on a per patient basis.

Quantitative assessment of atherosclerotic plaque burden on CCTA was performed using dedicated software (Autoplaque, Version 2.5, Cedars-Sinai Medical Center) as described previously (8). Coronary centerlines were extracted semi-automatically, and the proximal and distal aspects of each coronary segment were defined manually. Scan-specific thresholds were used to define plaque constituents and plaques were automatically identified, with manual adjustment as required. Total plaque volume was calculated on a per-patient basis for each of total, calcified, non-calcified and low attenuation plaque. Plaque burden was calculated by dividing plaque volume by the vessel volume of the region assessed, multiplying by 100 and summing on a per patient basis. Total plaque burden, calcified plaque burden, non-calcified plaque

burden and low-attenuation non-calcified plaque burden (<30 HU) were assessed. Plaque burden was used as the primary metric in this study as it takes into account differences in coronary artery size between patients and the fact that only segments with disease are analyzed to avoid introducing unnecessary noise from normal segments. A low-attenuation plaque burden greater than 4% was classified as high-risk based the cut-off value defined in our previous study (8). Pericoronary adipose tissue (PCAT) attenuation was measured in the proximal right coronary artery (PCAT-RCA, 10-50mm from the ostium), left anterior descending coronary artery (PCAT-LAD, 0-40mm from the bifurcation), and left circumflex (PCAT-LCx, 0-40mm from the bifurcation), where there was adequate image quality and luminal diameter equal to or greater than 2mm. PCAT attenuation was measured as the average attenuation of all adipose containing voxels (range -190 HU to -30 HU) within an outer radial distance from the vessel wall of 3mm (22).

Clinical Outcomes

Information on cardiovascular events and mortality were obtained from the SCOT-HEART database. Clinical events assessed were the following: percutaneous coronary intervention, coronary artery bypass graft, myocardial infarction, fatal or non-fatal myocardial infarction, cardiovascular death and all-cause mortality. This information was obtained from national coding data from the Data Research and Innovation Service of the National Health Services Scotland and was confirmed by review of the patient's electronic health records where required.

Statistical Analysis

Statistical analysis was performed using R, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Quantitative data are presented as mean ± standard deviation or, if not normally distributed, as median [interquartile range]. Statistical significance was assessed using Pearson Chi-square, Fishers exact, Students t, or Kruskal-Wallis tests as appropriate. Cohen's kappa was used to assess inter- and intra-observer agreement. Correlation was assessed with Spearman's rank correlation coefficient and regarded as very weak (<0.2), weak (0.20 to <0.40), moderate (0.40 to <0.60), strong (0.6 to <0.80), or very strong (0.8 to 1). Multivariable models were constructed to assess the impact of hepatosteatosis and cardiovascular risk factors on the presence of coronary artery disease, the presence of obstructive coronary artery disease, coronary artery calcium score and low-attenuation plaque burden. Models were constructed with the CT parameter, hepatosteatosis, and cardiovascular risk score. Further models were constructed with the CT parameter, hepatosteatosis, statin use recommended at baseline clinic assessment, cardiovascular risk factors which were significantly different in patients with hepatosteatosis (body mass index, hypertension, diabetes, hyperlipidemia) and with biologically plausible associations (age, gender). Calcium score was log transformed for inclusion in multivariable models. A statistically significant difference was defined as a two-sided *P* value < .05.

Results

Study Participants

The study consisted of 1726 participants (mean age, 58 ± 9 years; 974 men) in whom liver attenuation could be measured (Figure 1). Mean liver attenuation on non-contrast CT was 55 ± 13 HU. Inter-observer and intra-observer agreement for the identification of hepatosteatosis on CT was excellent (0.94 [95% CI: 0.82, 1.0] and 0.94 [95% CI: 0.83, 1.0], respectively). Compared with those without hepatosteatosis (91%, 1571/1726), participants with hepatosteatosis (9%, 155/1726) were of similar age (*P* = .99) but had a higher BMI, higher cardiovascular risk scores, and were more likely to have hypertension and diabetes mellitus (*P* < .001 for all, Table 1). There was no evidence of a difference in total cholesterol concentration in participants with and without hepatosteatosis, but those with hepatosteatosis had a lower high-density lipoprotein concentration (*P* = .007, Table 1).

Coronary Artery Calcification

Participants with hepatosteatosis on CT had a higher median coronary artery calcium score than participants without hepatosteatosis (43 [0 to 273] Agatston units (AU) versus 19 [0 to 225] AU; *P* = .046). Similarly, participants with hepatosteatosis were less likely to have a coronary artery calcium score of zero compared with those without hepatosteatosis (28% [44/155] versus 37% [580/1571]; p=0.03; Figure 2). However, we found no evidence of a difference in the prevalence of hepatosteatosis across calcium score groups (Table 2). Furthermore, hepatosteatosis was not an independent predictor of coronary artery calcium score when adjusting for cardiovascular risk score (exp(β), 0.89 [95% CI: 0.49, 1.63]; *P* = .72) or cardiovascular risk factors and statin

recommended at baseline clinic assessment (exp(β), 1.23 [95% CI: 0.72, 2.11]; *P* = 0.45) (Figure E1).

Visual Assessment of CCTA

Participants with non-obstructive and obstructive disease had lower liver attenuation compared with participants with normal coronary arteries (53 ± 14 HU and 54 ± 13 HU versus 57±13 HU, respectively; *P* < .001 for both; Figure 3). Participants with hepatosteatosis were less likely to have normal coronary arteries (28% [43/155] versus 37% [582/1571]) and were more likely to have non-obstructive disease (48% [74/155] versus 37% [583/1571]), although they had a similar frequency of obstructive disease compared with participants without hepatosteatosis (Figure 2; 25% [38/155] versus 26% [405/1571]). In an unadjusted analysis, hepatosteatosis was a predictor of the presence of coronary artery disease on CT (odds ratio [OR], 1.54 [95% CI 1.07, 2.24]; *P* = .02), but this was not independent of conventional cardiovascular risk factors or statin use recommended at the baseline clinic in a multivariable model (Figure 4). Hepatosteatosis was not a predictor of the presence of obstructive coronary artery disease on CT in unadjusted (OR, 0.94 [95% CI: 0.63, 1.36]; *P* = .73) or multivariable (Figure 4) analyses. There was no evidence of a difference in the frequency of visually assessed adverse plaques or adverse plaque characteristics between participants with and without hepatosteatosis (Table 2).

Quantitative Plaque Assessment

There was no evidence of a difference in total, non-calcified, calcified, or low attenuation plaque volume between patients with or without hepatosteatosis (Supplementary Table 1). There was no evidence of a difference in total plaque burden

or burden of calcified or non-calcified plaque in participants with hepatosteatosis (Table 3). However, low-attenuation plaque burden was higher in participants with hepatosteatosis (low-attenuation plaque burden 5.1% [0 to 7.2] versus 4.1% [0 to 6.8]; *P* = .04; Figure 3). Participants with hepatosteatosis were also more likely to have a low-attenuation plaque burden greater than the pre-defined cut-off value of 4% (59% of participants [92/155] versus 51% of participants [795/1571]; *P* = .04). However, hepatosteatosis was not an independent predictor of low-attenuation plaque burden when adjusted for cardiovascular risk score (exp(β), 1.13 [95% CI: 0.57, 2.24]; *P* = .72) or cardiovascular risk factors and statin recommended at the baseline clinic (exp(β), 1.38 [95% CI: 0.70, 2.71]; *P* = 0.35; Figure E2). There was a strong correlation between low attenuation plaque burden and coronary artery calcification (r 0.62, *P* = .001). Participants with hepatosteatosis had lower PCAT attenuation around the left coronary artery, left circumflex artery and right coronary artery and were less likely to have PCAT equal to or greater than -70.5 HU in the right coronary artery (Table 2).

Clinical Outcomes and Hepatosteatosis

Over a median of 4.7 [4.0 to 5.7] years, fatal or non-fatal myocardial infarction occurred in 41 participants. There was no evidence of a difference in the frequency of fatal or non-fatal myocardial infarction in participants with and without hepatosteatosis (1.9% [3/155] versus 2.4% [38/1571]; *P* = .920). There was also no evidence of a difference in the frequency of percutaneous coronary intervention, coronary artery bypass grafting, cardiovascular mortality or all-cause mortality (Table 4).

Discussion

This study aimed to assess the association between hepatosteatosis and atherosclerotic plaque on CT. We found that hepatosteatosis is common on cardiac CT, identified in 9% of SCOT-HEART participants. Participants with hepatosteatosis had a more coronary artery disease, including a higher coronary artery calcium score (43 AU versus 19 AU, *P* = .046), more non-obstructive coronary artery disease (48% versus 37%, *P* = .02), and an increased burden of low-attenuation plaque (5.11% versus 4.07%, *P* = .04). However, these findings are largely attributable to the presence of co-existing cardiovascular risk factors, as hepatosteatosis was not an independent predictor of these findings. In particular hepatosteatosis was not an independent predictor of low-attenuation plaque burden when adjusted for cardiovascular risk score (exp(β), 1.13 [95% CI: 0.57, 2.24]; *P* = .72).

Hepatosteatosis is an established risk factor for the presence of subclinical cardiovascular disease (2, 23, 24). The mechanisms underlying this are uncertain, but involve insulin resistance, altered lipid metabolism, inflammation, oxidative stress, and endothelial and microvascular dysfunction. We found that hepatosteatosis was associated with increased low-attenuation plaque burden, possibly secondary to overlapping risk factors such as inflammation, insulin resistance and altered lipid metabolism. However, this association between hepatosteatosis and coronary artery calcification, obstructive disease, and low-attenuation plaque burden was not independent of cardiovascular risk factors. Moreover, participants with hepatosteatosis had lower PCAT attenuation and were less likely to have PCAT above the previously proposed risk threshold. Together, our findings suggest that whilst

hepatosteatosis was associated with coronary artery disease, this is mediated through its co-association with cardiovascular risk factors.

Hepatosteatosis is a frequent finding occurring on between 17 and 25% of CT scans in the United States (5, 25). In our study the frequency was lower, likely representing differences in the underlying demographics and risk factors in our population. Similar to other studies, we found that diabetes, BMI and hypertension were particularly important predictors of the presence of hepatosteatosis on CT. Hepatosteatosis overlaps with features of metabolic syndrome including obesity, hypertension, hyperglycemia, dyslipidemia and inflammation. In women, female-specific factors also influence the development, phenotype and natural history of NAFLD (26). We found that patients with hepatosteatosis had a higher BMI compared to those without hepatosteatosis, but BMI was not an independent predictor of coronary artery disease on CT. This is likely due to the overlap between these various risk factors in the development of coronary artery disease.

We found that the hepatosteatosis was not associated with myocardial infarction over 5 years of follow-up. However, PROspective Multicentre Imaging Study for Evaluation of chest pain (PROMISE) found that hepatosteatosis was identified in 25% of participants and was associated with an increased risk of major adverse cardiovascular event (MACE) (hazard ratio 1.69 [95% CI: 1.16, 2.48]; $P = .006$), which persisted after adjusting for cardiovascular risk score, metabolic syndrome and obesity (25). Similarly, Early-Identification of Subclinical Atherosclerosis by Noninvasive Imagining Research (EISNER) showed that metabolic syndrome, hepatosteatosis and epicardial adipose tissue were all predictive of MACE (27). In contrast, large cohort

studies have failed to show an association between hepatosteatosis and mortality that is independent of other cardiovascular risk factors (28-30). A large matched cohort of over 120,000 patients with NAFLD or non-alcoholic hepatosteatosis, found that patients were not at increased risk of stroke or myocardial infarction after adjustment for cardiovascular risk factors (30). These discordant findings may be secondary to differences in outcome measures such as the inclusion of unstable angina, differences in hepatosteatosis prevalence, or residual confounding factors which were not assessed. Our data, in combination with prior studies, therefore suggest that whilst hepatosteatosis is associated with coronary artery disease, it may not be an independent risk factor for cardiovascular disease but rather represents a hepatic manifestation of cardiometabolic disease.

Limitations of this study include the selection of patients and small number of subsequent cardiovascular events. This was a post-hoc analysis of previously collected data; therefore, no formal power calculation was performed. Whilst we are confident that we have not missed a strong relationship between hepatosteatosis and cardiovascular events, the study does not have adequate power to exclude more subtle associations, and larger studies are warranted. Additionally, study participants represented those undergoing assessment of suspected coronary artery disease, rather than the general population or those with proven NAFLD, so extrapolation to other cohorts should be made with caution. Information on alcohol consumption, triglyceride concentration, inflammatory biomarkers, waist circumference and pre-existing liver disease was not available. Furthermore, hepatosteatosis was identified based on CT findings rather than liver biopsy. Another limitation is that we assessed only liver attenuation, whereas other studies have also used the difference between

liver and spleen attenuation. Finally, only total cholesterol level and high-density lipoprotein cholesterol concentrations are available in the SCOT-HEART database, and associations between hepatosteatosis and low-density lipoprotein cholesterol concentrations were therefore not possible.

In conclusion, we have shown that hepatosteatosis is common in patients undergoing CCTA. Hepatosteatosis was associated with an increased burden of low-attenuation atherosclerotic plaque on CT, but this was not independent of traditional cardiovascular risk scores. Furthermore, the presence of hepatosteatosis did not appear to be a predictor of subsequent myocardial infarction.

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Tables

Table 1: Characteristics of Participants With and Without Hepatosteatosis on CT

		Hepatosteatosis on CT	
		No	**Yes**
n		1571 (91)	155 (9)
Men		878 (56)	96 (62)
Age (y)		58 ± 9	58 ± 9
BMI (kg/m^2)		29 ± 5	33 ± 6
Atrial fibrillation		29 (2)	4 (3)
Previous CHD		161 (10)	15 (10)
Previous CVD		66 (4)	11 (7)
Previous PAD		30 (2)	1 (1)
Smoking status	Current smoker	294 (19)	33 (21)
	Ex-smoker	519 (33)	60 (39)
	Non-smoker	757 (48)	62 (40)
Hypertension		518 (33)	75 (49)
Diabetes mellitus		157 (10)	38 (25)
Family history CHD		674 (43)	71 (46)
Total cholesterol concentration (mg/dL)		193 ± 71	191 ± 79
High-density lipoprotein concentration (mg/dL)		38 ± 27	32 ± 23
Anginal symptoms	Atypical angina	383 (24)	42 (27)
	Non-anginal	610 (39)	58 (37)
	Typical angina	578 (37)	55 (36)
Cardiovascular risk score		17 ± 11	23 ± 13

Note.—Data presented as *number (%); mean ± standard deviation. BMI = body mass index, CHD = coronary heart disease, PAD = peripheral arterial disease, CVD = cerebrovascular disease*

Table 2: CT Findings in Participants With and Without Hepatosteatosis

		Hepatosteatosis on CT		p
		No	Yes	
Number		1571	155	-
Coronary artery calcium score (AU)		19 [0 to 225]	43 [0 to 273]	.046 *
Coronary artery calcium score group	0 AU	580 (37)	44 (28)	.08
	1-100 AU	453 (29)	48 (31)	
	101-400 AU	262 (17)	35 (23)	
	400-1000 AU	151 (10)	11 (7)	
	>1000 AU	126 (8)	17 (11)	
CCTA	Normal	583 (37)	43 (28)	.02 *
	Non obstructive	583 (37)	74 (48)	
	Obstructive	405 (26)	28 (25)	
Visually assessed adverse plaques		544 (35)	50 (32)	.61
	Positive remodeling	539 (34)	50 (32)	.67
	Low-attenuation plaque	147 (9)	17 (11)	.61
	Spotty calcification	268 (17)	25 (16)	.86
	Napkin ring sign	63 (4)	11 (7)	.11
PCAT	Left coronary artery	-76.85 ± 7.79	-78.44 ± 7.79	.02 *
	Left circumflex artery	-73.02 ± 7.64	-75.40 ± 8.04	.001 *
	Right coronary artery	-75.73 ± 8.35	-77.39 ± 7.55	.03 *
	PCAT-RCA ≥-70.5 HU	365 (26)	21 (16)	.01 *

*Note.—Data presented as number (%), median [interquartile range], or mean ± standard deviation. * indicates a statistically significant p-value <0.05.*

AU = Agatston Units, CACS = coronary artery calcium score, CCTA = coronary CT angiography, PCAT = pericoronary adipose tissue attenuation, RCA = right coronary artery

Table 3: Quantitative Plaque Analysis in Participants With and Without Hepatosteatosis on CT

	Hepatosteatosis on CT		**p**
	No	**Yes**	
Total plaque burden (%)	38.86 [0 to 49.33]	41.85 [0 to 49.26]	.07
Calcified plaque burden (%)	0.37 [0 to 2.75]	0.63 [0 to 2.88]	.13
Non-calcified plaque burden (%)	35.25 [0 to 45.16]	37.43 [0 to 46.66]	.08
Low-attenuation plaque burden (%)	4.07 [0 to 6.84]	5.11 [0 to 7.16]	.04 *

*Note.—Data presented as median [interquartile range]. * indicates a statistically significant p-value <0.05.*

Table 4: Clinical Outcomes in Participants With and Without Hepatosteatosis on CT

	Hepatosteatosis on CT		**p**
	No	**Yes**	
Number	1571	155	-
Percutaneous coronary intervention	170 (11)	19 (12)	.68
Coronary artery bypass graft	58 (4)	4 (3)	.63
Myocardial infarction	35 (2)	3 (2)	>.99
Fatal or non-fatal myocardial infarction	38 (2)	3 (2)	.92
Cardiovascular death	4 (0.3)	0	>.99
All cause death	33 (2)	3 (2)	>.99

Note.—Data presented as number (%).

Figures

Figure 1: Flow-diagram showing the number of participants and those excluded.

Note.—SCOT-HEART = Scottish Computed Tomography of the Heart

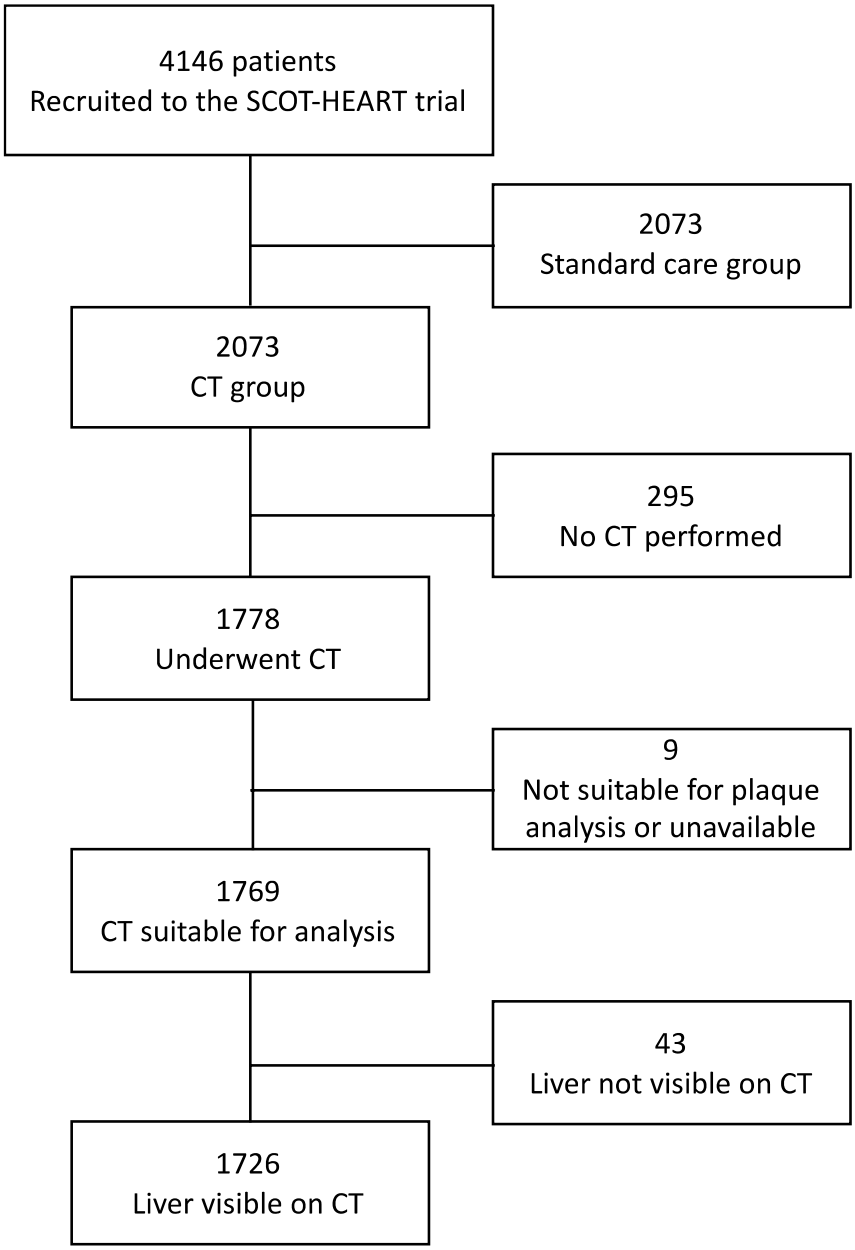


Figure 2: Proportion of participants with (red) and without (blue) hepatosteatosis on CT in (A) participants with different coronary artery calcium scores on non-contrast CT and (B) participants with normal, non-obstructive or obstructive disease on coronary CT angiography (CCTA).

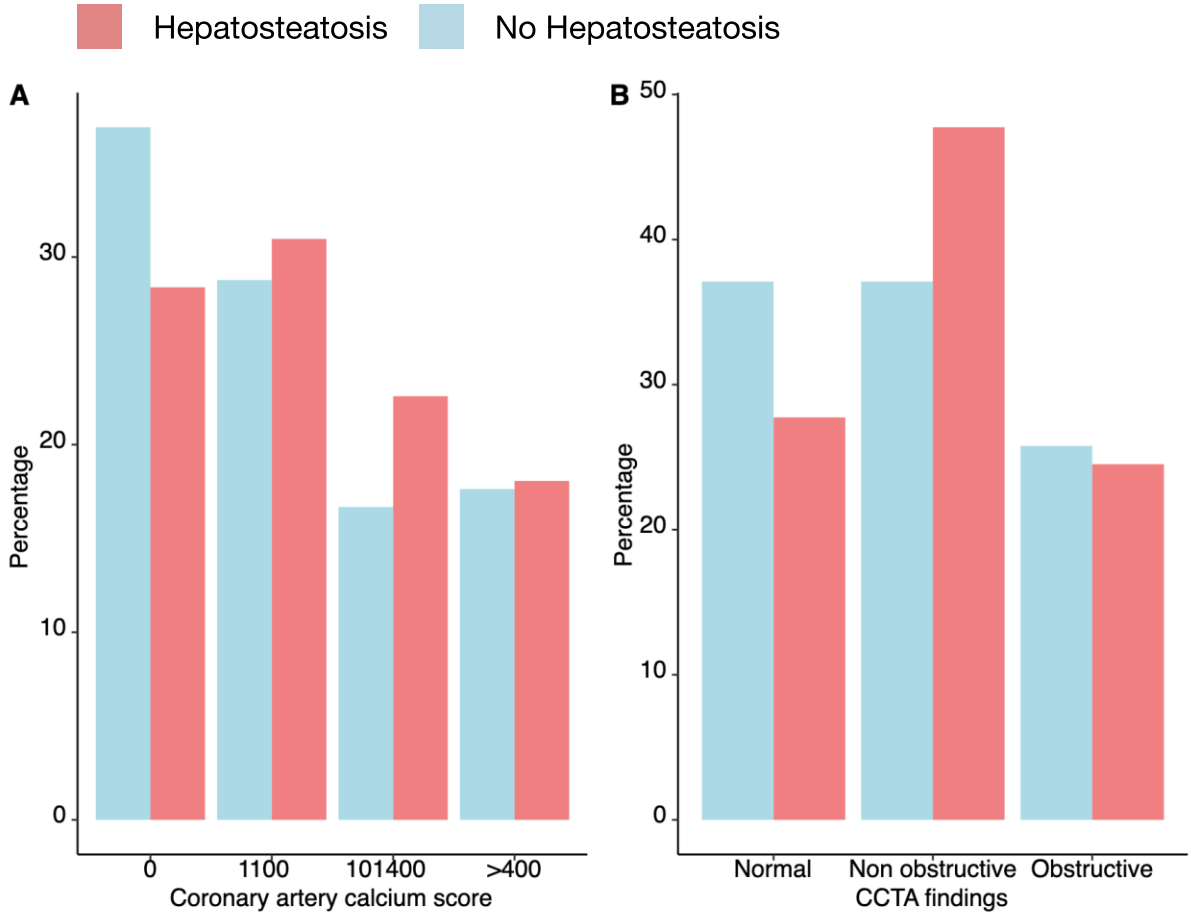


Figure 3: Liver attenuation in participants with normal, non-obstructive or obstructive disease on coronary CT angiography (CCTA). The box indicates median and interquartile range, the whiskers indicate 1.5 times the nearest interquartile range, and dots represent outliers. HU = Hounsfield units

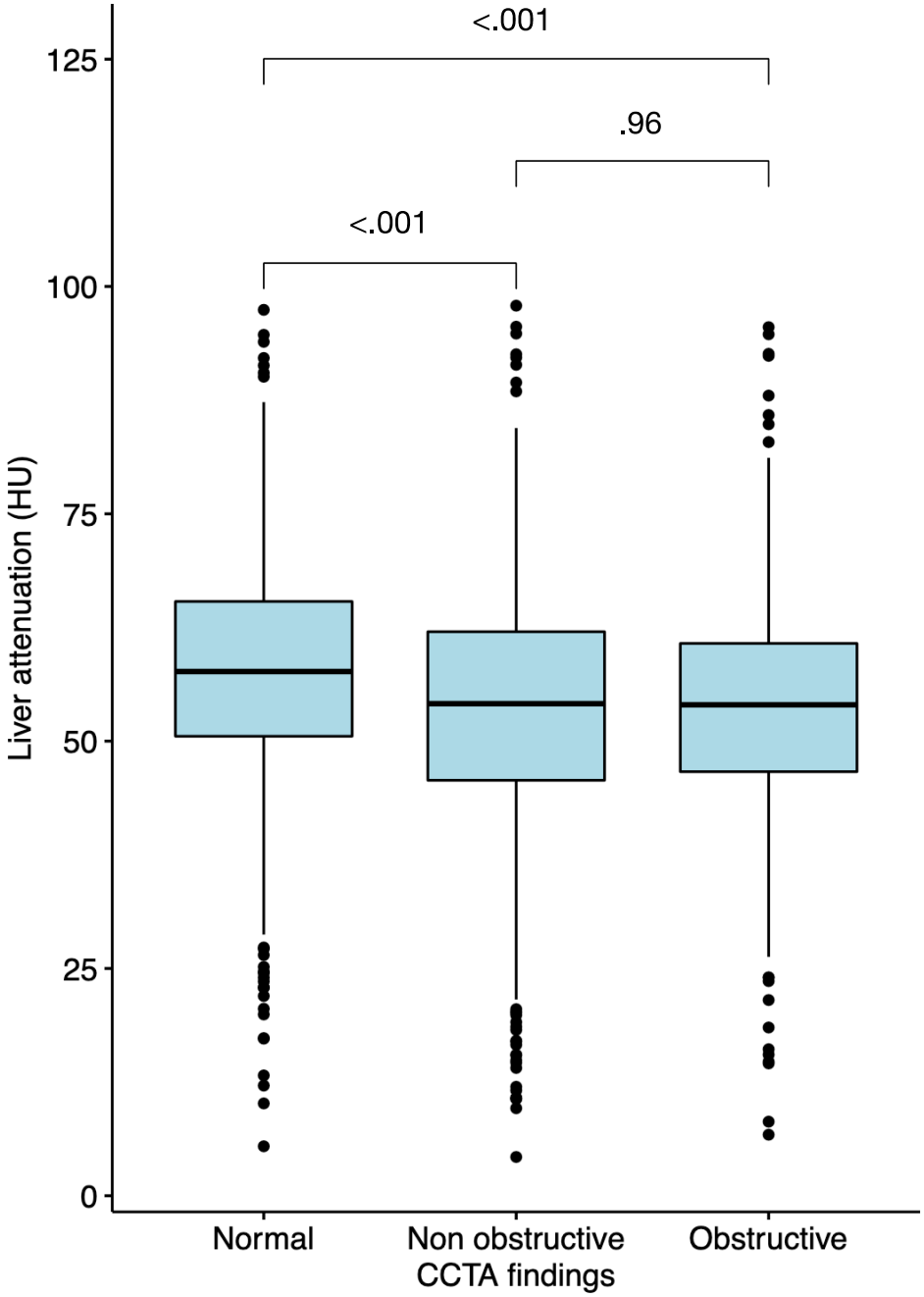


Figure 4: Multivariable model of cardiovascular risk factors and hepatosteatosis for the presence of any coronary artery disease on CT and obstructive coronary artery disease on CT.

* <0.05 ; ** <0.01 ; *** <0.001

Note.—Statin refers to statin use recommended after the baseline cardiology clinic assessment.

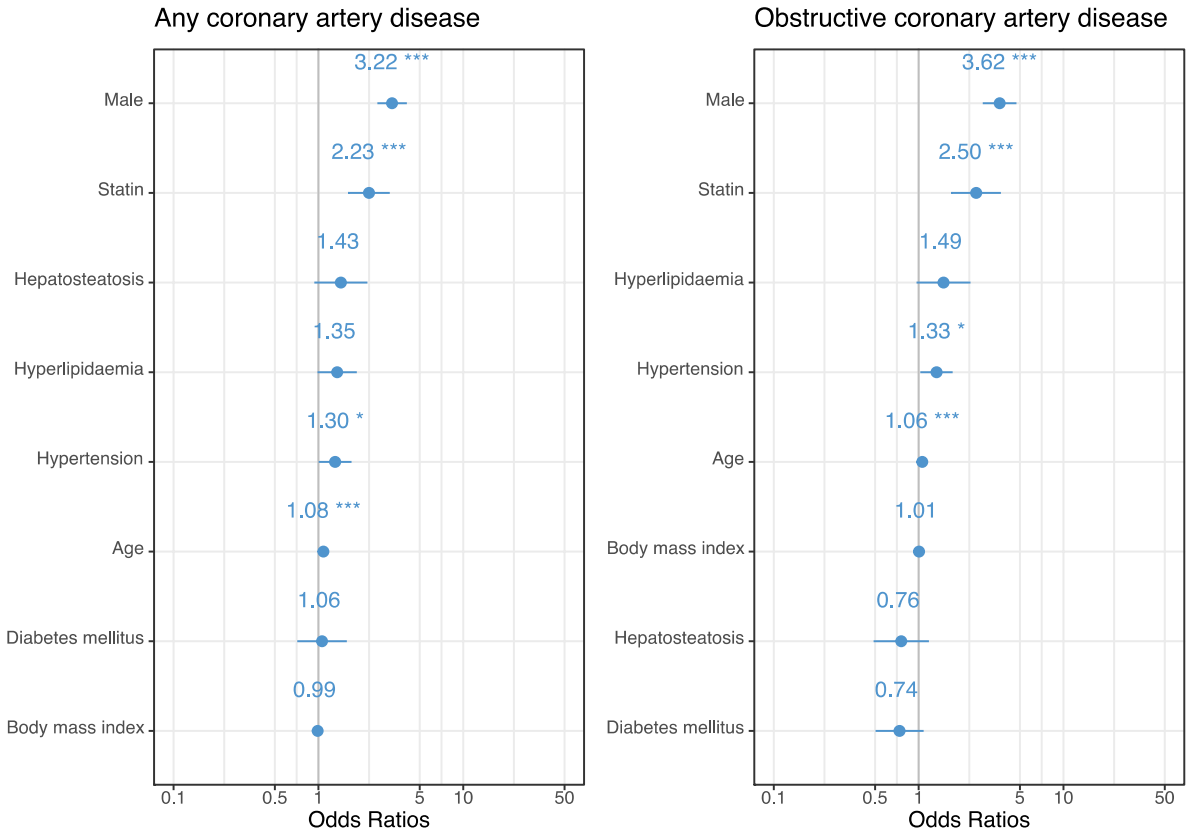
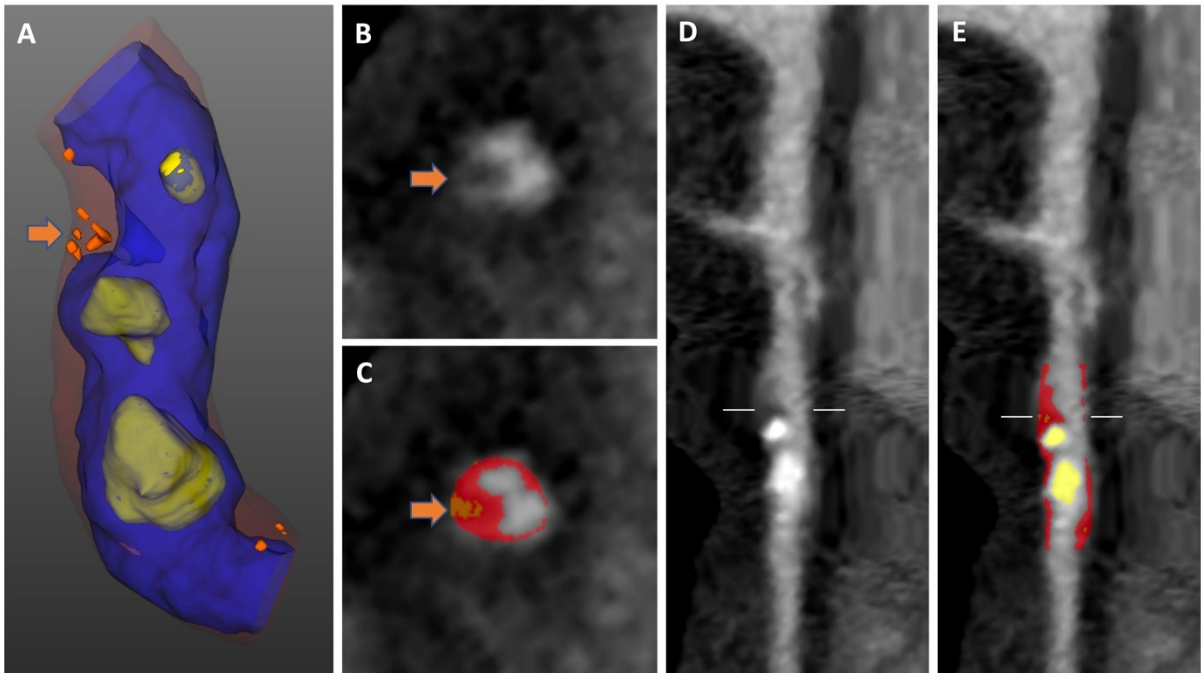


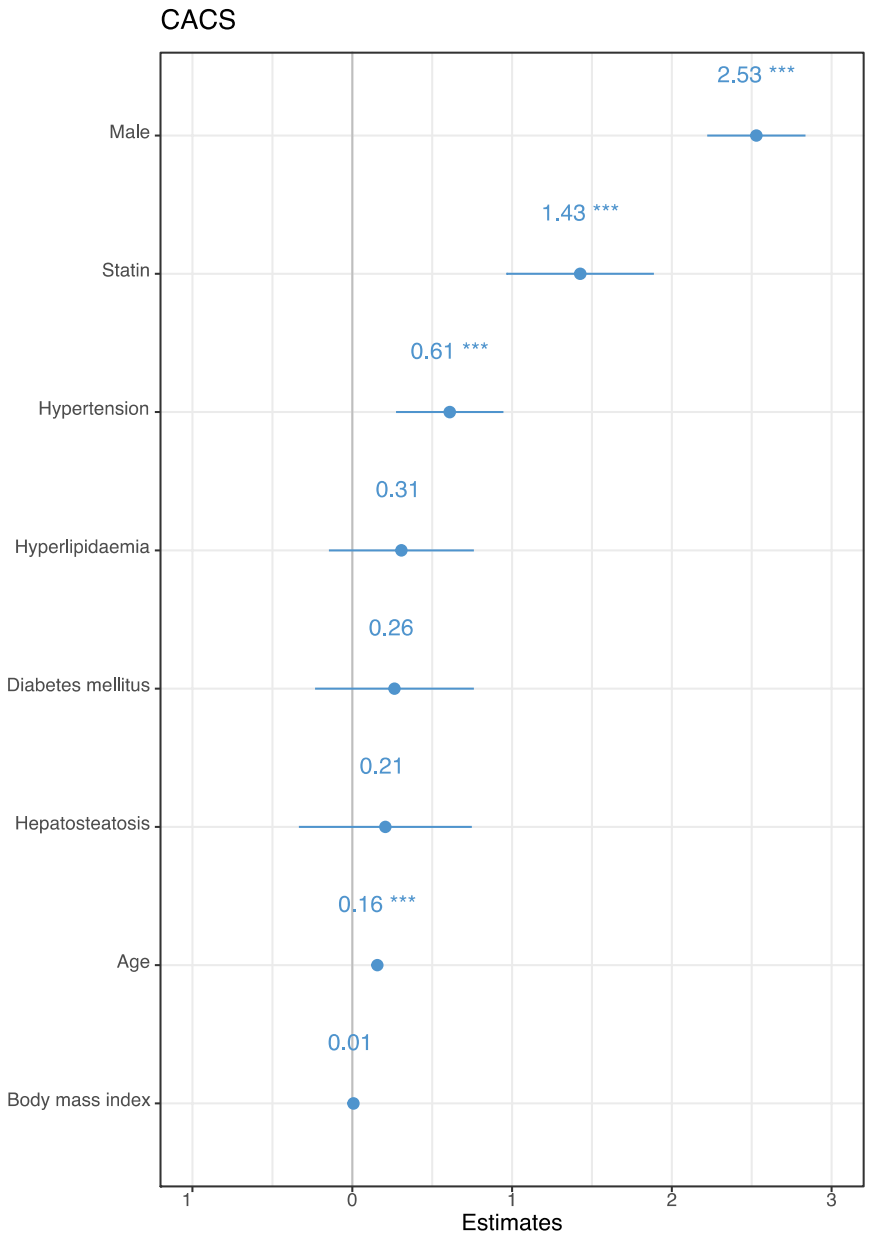
Figure 5: Coronary CT angiography images from a 52-year-old man with type 2 diabetes mellitus who had hepatosteatosis on CT (liver attenuation 29 Hounsfield units). (A) Image shows a three-dimensional reconstruction with low-attenuation non calcified plaque in orange highlighted by the arrow. The low-attenuation plaque burden was greater than 4%. (B-C) Images show an axial cross section of the proximal left anterior descending coronary artery with the arrow highlighting the low-attenuation non calcified plaque. (D-E) Images are curved planar reformations showing mixed plaque in the left anterior descending coronary artery. Reference lines denote the position of axial images B/C. Yellow shows calcified plaque; red shows non-calcified plaque; orange shows low-attenuation non calcified plaque; and blue shows the coronary lumen.



Supplementary information

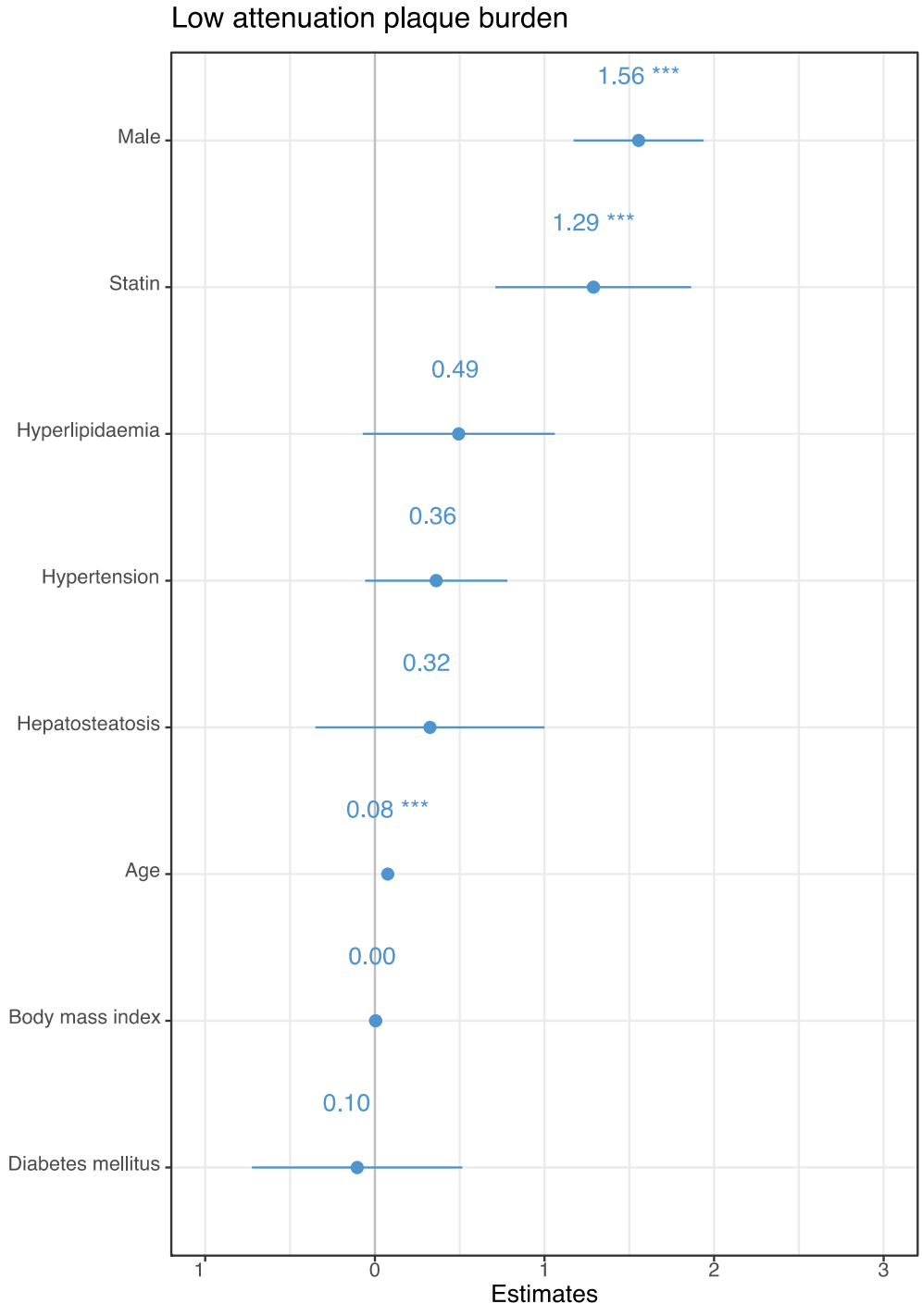
Supplementary Figure 1: Multivariable model of cardiovascular risk factors and hepatosteatosis for the coronary artery calcium score (CACS).

* <0.05 ; ** <0.01 ; *** <0.001



Supplementary Figure 2: Multivariable model of cardiovascular risk factors and hepatosteatosis for the low attenuation plaque burden.

* <0.05 ; ** <0.01 ; *** <0.001



Supplementary Table 1: Quantitative Plaque Analysis in Participants With and Without Hepatosteatosis on CT

	Hepatosteatosis on CT		p
	No	**Yes**	
Total plaque volume (%)	271 [0, 802]	368 [0, 944]	.07
Calcified plaque volume (%)	3 [0, 45]	6 [0, 50]	.15
Non-calcified plaque volume (%)	258 [0, 736]	354 [0, 845]	.08
Low-attenuation plaque volume (%)	34 [0, 107]	44 [0, 130]	.05

Note.—Data presented as median [interquartile range].