

The role of lipoprotein(a) in predicting coronary artery disease among ageing endurance athletes and healthy controls

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Aims

Ageing endurance athletes have a higher prevalence of coronary artery disease (CAD) on coronary computed tomography angiography than healthy controls, despite similarly low conventional cardiovascular (CV) risk. The predictive value of lipoprotein(a) [Lp(a)] for CAD in these low-risk individuals remains unclear.

Methods and results

The Master@Heart study included 558 men (aged 45–70 years) without known CV risk factors: 191 lifelong athletes, 191 late-onset athletes, and 176 healthy controls. Coronary computed tomography angiography assessed coronary artery calcification (CAC) and plaques. The association between Lp(a) and subclinical CAD was assessed using logistic regression analysis to estimate odds ratios (ORs), adjusted for CV risk factors. Lipoprotein(a) was analysed dichotomously (<125 vs. >125 nmol/L) and continuously (per 10 nmol/L increase). Seventy-six participants (13.6%) had elevated Lp(a) levels (>125 nmol/L). Elevated Lp(a) was significantly associated with age-specific CAC percentile ≥ 75 (OR 1.80, $P = 0.049$) and ≥ 1 mixed plaque (OR 1.76, $P = 0.046$). Other CAD measures all tended to be more prevalent in those with elevated Lp(a). In the continuous analysis, Lp(a) was significantly associated with CAC > 100 (OR 1.03, $P = 0.045$), CAC percentile ≥ 75 (OR 1.04, $P = 0.014$), and ≥ 1 mixed or non-calcified plaque (OR 1.03, $P = 0.029$). Lipoprotein(a) and prevalence of elevated Lp(a) were similar across lifelong athletes, late-onset athletes, and controls ($P = 0.586$ and $P = 0.724$, respectively). No significant interaction was found between Lp(a) and the exercise groups in predicting CAD.

Conclusion

Lipoprotein(a) is independently associated with subclinical CAD in ageing endurance athletes and healthy controls, despite similarly low conventional CV risk. Lipoprotein(a) does not explain the higher CAD prevalence in lifelong athletes compared with controls, but may enhance risk stratification in this low-risk population.

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Executing institution: Multicentre Master@Heart study in Jessa Hospital Hasselt, University Hospitals Leuven and Antwerp University Hospital

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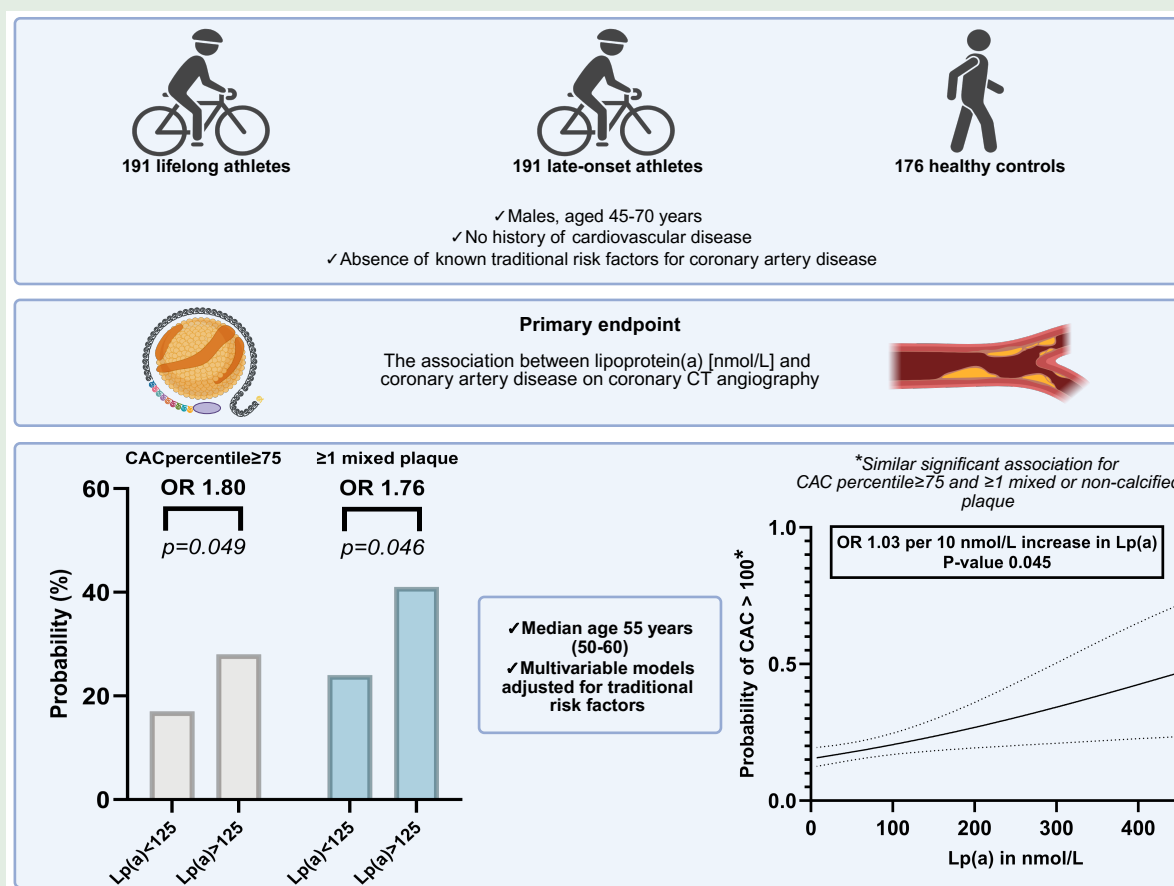
Registration

ClinicalTrials.gov: NCT03711539

Lay summary

Elevated lipoprotein(a) [Lp(a)] levels, both at the clinically relevant threshold (>125 nmol/L) and measured continuously, are linked to coronary atherosclerosis on computed tomography imaging in both ageing endurance athletes and healthy controls, even when they have no traditional cardiovascular (CV) risk factors.

- Elevated Lp(a) (>125 nmol/L) was independently associated with increased coronary artery calcification and the presence of at least one mixed coronary plaque.
- Lipoprotein(a) may help identify hidden coronary atherosclerosis in low-risk individuals and support more personalized CV assessments.

Graphical Abstract

CT, computed tomography; OR, odds ratio; Lp(a), lipoprotein(a); CAC, coronary artery calcification.

Keywords

Lipoprotein(a) • Ageing endurance athletes • Coronary artery disease • Coronary computed tomography angiography • Cardiovascular risk stratification

Introduction

While the cardiovascular (CV) benefits of regular physical activity are well established,¹ the relationship between lifelong high-volume endurance exercise dose and coronary artery disease (CAD) is complex. Recent studies, including the Master@Heart study, have shown a higher prevalence of coronary plaques and coronary artery calcification (CAC) in ageing endurance athletes compared with healthy non-athletes, even after excluding individuals with known traditional CV risk factors such as

smoking, arterial hypertension, dyslipidaemia, overweight, or diabetes mellitus.²⁻⁴ Moreover, the Master@Heart study identified a higher prevalence of less favourable plaque phenotypes, namely non-calcified and mixed plaques among endurance athletes.⁴⁻⁶

Considering the challenges in CV risk stratification among individuals without traditional risk factors, alternative biomarkers such as lipoprotein(a) [Lp(a)] may offer valuable prognostic information. Lipoprotein(a), a LDL-like particle, has gained increasing recognition in recent atherosclerosis and CV prevention guidelines as an independent risk factor for

atherosclerotic CV disease, even in individuals with low LDL cholesterol levels.^{7,8} Lipoprotein(a) concentrations are largely genetically determined (>90%), remain relatively stable across the lifespan, and have prompted recommendations for a one-time measurement in all adults.^{7,8} Notable ethnic differences exist, with Lp(a) levels being lowest in White and East-Asian populations and highest among individuals of African descent.⁹ The distribution is skewed in populations with low Lp(a) levels, with a long right-sided tail representing individuals with markedly elevated concentrations.⁹ Although the relationship between Lp(a) and CAD is continuous, both the American Heart Association and the European Atherosclerotic Society define Lp(a) levels >125 nmol/L as elevated.^{7,8} Measuring Lp(a) may refine CV risk stratification and inform decisions regarding early and intensified preventive strategies.⁸ However, the predictive value of elevated Lp(a) levels for CAD in ageing endurance athletes and healthy controls without traditional CV risk factors remains unclear.

This study aimed to investigate the association between Lp(a) and the presence and characteristics of CAD in ageing endurance athletes and healthy controls without known CV risk factors. Specifically, we assessed the relationship between Lp(a) levels and CAC, coronary plaque presence, and plaque phenotype as determined by coronary computed tomography angiography (CCTA).

Methods

Study design and population

The study design and methodology of the Master@Heart study have been described in detail previously.^{4,10} In brief, this prospective, multicentre cohort study was conducted at three hospitals in Belgium: Jessa Hospital (Hasselt), Antwerp University Hospital, and University Hospitals Leuven.

Eligible participants were men aged 45–70 years, selected to reflect a spectrum of lifelong physical activity exposure. Athletes were required to engage in regular endurance exercise, either cycling or triathlon for ≥8 h per week, or running for ≥6 h per week, starting at least 6 months prior to baseline evaluation.⁴ Lifelong athletes initiated regular endurance training before the age of 30, whereas late-onset athletes started after the age of 30. Non-athletic controls engaged in <3 h of physical activity per week and had no history of intensive endurance exercise.

Exclusion criteria included a history of CV disease, known allergy to iodine-based contrast agents, and any known traditional CV risk factors: smoking or former smoking, arterial hypertension, dyslipidaemia, diabetes mellitus, or a body mass index (BMI) > 27.2 kg/m².

A total of 605 participants were randomly selected, of whom 558 remained after excluding 47 individuals who met one or more exclusion criteria. Participants were stratified into three predefined age groups: young, 45–53 years (*n* = 256); middle-aged, 54–62 years (*n* = 233); and old, 63–70 years (*n* = 69).¹⁰ The targeted recruitment ratio—3:3:1 across the three age groups—was established in the study design to reflect the declining prevalence of high-volume endurance exercise with advancing age and was applied similarly across the three exercise groups.¹⁰

Cardiopulmonary exercise testing

Cardiorespiratory fitness was assessed based on peak oxygen uptake (VO₂peak) with a continuous, incremental cycling stress test.¹⁰ Respiratory gas exchange was measured using a breath-by-breath open-circuit spirometry system, with VO₂peak defined as the highest 30 s average of oxygen uptake.

Training load

Participants completed a questionnaire to estimate lifelong training load regarding sports type, training duration and intensity. Metabolic equivalent of task-minutes (MET-min) per week were calculated as a measure of training

load by multiplying the MET score of a sports activity by the weekly exercise duration in minutes.¹¹

Coronary computed tomography angiography

Coronary computed tomography angiography was executed using a 128-slice dual-source CT scanner (Siemens Somatom Force—Siemens Healthineers, Forchheim, Germany), a 256-slice CT scanner (GE Revolution—GE Healthcare, Milwaukee, WI, USA), or a 320-slice CT scanner (Aquilion ONE VISION—Canon Medical Systems, Otawara, Japan). Esmolol was given intravenously as required to maintain a heart rate below 65 b.p.m.. Two minutes before the scan, all participants received 0.4 mg of sublingual nitroglycerine. Coronary calcium was first quantified using the Agatston method, generating the CAC score (expressed in Agatston units). Following this, a CCTA was conducted to assess coronary plaques, utilizing an intravenous injection of iodinated contrast medium through a peripheral vein, followed by a saline flush.

Coronary plaques were evaluated using Syngo.Via (Siemens Healthineers, Forchheim, Germany) or GE Advanced Workstation (GE Healthcare, Milwaukee, WI, USA) software. Coronary computed tomography angiography interpreters were blinded to participants' exercise history and other study assessments. Plaque analysis followed the 2016 SCCT guidelines, considering location, stenosis severity, and composition (calcified, non-calcified or mixed).¹² Calcified plaques consisted entirely of calcified regions with a density exceeding 130 Hounsfield units. Non-calcified plaques lacked any calcification, while mixed plaques contained both calcified and non-calcified components.^{12,13}

Lipoprotein(a) measurement

Plasma concentrations of Lp(a) were measured at baseline using an immunoturbidimetric assay on the Cobas c502 analyser (Roche Diagnostics, Mannheim, Germany). This assay, calibrated in nmol/L, reflects the molar concentration of Lp(a) particles and minimizes the influence of apolipoprotein(a) isoform size heterogeneity, a known confounder in mass-based assays. According to the manufacturer and prior validations, Lp(a) values obtained with this method are minimally or not affected by apolipoprotein(a) size polymorphisms. The measurements were performed in the central laboratories of KU Leuven and Jessa Hospital (Hasselt) following standardized protocols, with samples analysed in batch to reduce inter-assay variability.

Endpoints and hypothesis

The primary objective of this analysis was to examine the relationship between Lp(a) levels and CAD in the Master@Heart study. We hypothesized that elevated Lp(a) levels, particularly levels >125 nmol/L, would be independently associated with the presence of CAD in this ostensibly healthy, physically active male cohort. In addition to evaluating Lp(a) dichotomously, we also assessed its relationship with CAD as a continuous variable. In this study, CAD was defined as the presence of elevated CAC and/or atherosclerotic plaques (calcified, non-calcified, or mixed) detected on CCTA.

Statistical analysis

A comprehensive explanation of the rationale behind the initial sample size is available elsewhere.^{4,10} Statistical analysis was performed with SPSS statistics (version 29.0.2.0) and figures were created with GraphPad Prism (version 10.4.1). Normality was assessed using the Shapiro–Wilk test.

Continuous variables were reported as mean ± standard deviation or median with interquartile range, depending on normality; categorical variables as counts with percentages. Group differences in continuous variables were assessed using independent samples *t*-test or Mann–Whitney *U* test for two groups, and one-way ANOVA or Kruskal–Wallis test for three groups, as appropriate. Categorical variables were compared using χ^2 test. Due to the skewed distribution of Lp(a), geometric means with 95% confidence intervals (CIs) were reported; however, log-transformation did not normalize the data, so non-parametric tests were used.

The association between Lp(a) levels and binary CAD measures was analysed using multiple logistic regression to estimate odds ratios (ORs) with 95% CIs, adjusting for traditional CV risk factors including age, LDL

Table 1 Demographics and exercise characteristics stratified by lipoprotein(a) group

	Lp(a) < 125 (n = 482)	Lp(a) > 125 (n = 76)	P-value
Demographics			
White ethnicity—n(%)	482 (100.0)	76 (100.0)	
Lifelong athletes—n(%)	168 (34.9)	23 (30.3)	0.433
Late-onset athletes—n(%)	164 (34.0)	27 (35.5)	0.798
Controls—n(%)	150 (31.1)	26 (34.2)	0.590
Lp(a) (nmol/L)	17.3 (16.0–18.7)	194.0 (180.8–208.0)	<0.001
Age (years)	54.6 (49.4–59.8)	56.4 (50.4–62.0)	0.097
Height (cm)	178.8 (±6.5)	179.7 (±5.9)	0.229
Weight (kg)	75.0 (69.7–80.8)	77.2 (69.5–82.0)	0.360
BMI (kg/m ²)	23.6 (22.1–25.1)	23.8 (22.1–25.1)	0.889
Heart rate (b.p.m.)	54 (49–60)	56 (50–60)	0.300
BP systolic (mmHg)	122.0 (115.0–130.0)	126.5 (117.0–137.8)	0.038
BP diastolic (mmHg)	75.5 (70.0–80.0)	78.0 (70.0–85.0)	0.030
Total cholesterol (mg/dL)	191.0 (169.0–212.0)	207.6 (195.0–231.0)	<0.001
LDL cholesterol (mg/dL)	123.0 (104.0–142.0)	138.0 (117.0–160.0)	<0.001
HDL cholesterol (mg/dL)	62.0 (53.0–71.6)	64.2 (56.1–77.5)	0.039
Triglycerides (mg/dL)	79.0 (62.0–99.0)	84.5 (68.0–101.0)	0.180
HbA1c (%)	5.4 (5.3–5.6)	5.4 (5.3–5.6)	0.886
Family history of CAD—n(%)	33 (6.8)	3 (4.0)	0.339
Exercise characteristics			
Hours exercise per week	10 (3–12)	9 (3–12)	0.597
Years of endurance exercise	19.7 (6.9–34.8)	23.3 (13.5–35.8)	0.184
MET-min/week	4500.0 (1333.5–5400.0)	4050.0 (1350.0–4972.5)	0.524
VO ₂ peak (mL/min/kg)	44.0 (38.0–49.7)	43.8 (39.0–49.0)	0.683
VO ₂ peak predicted (%)	148.0 (123.9–166.2)	149.8 (129.0–165.6)	0.853

Bold values indicated statistical significance.

Data are presented as medians with interquartile ranges or means ± standard deviations. Categorical variables are reported as n(%), with percentages reflecting the proportion within each Lp(a) category. Due to its skewed distribution, Lp(a) is shown as a geometric mean with 95% CI.

BP, blood pressure.

cholesterol, HDL cholesterol, HbA1c, systolic and diastolic blood pressure, BMI, physical activity (MET-min/week), and family history of CAD (defined as a first-degree relative with myocardial infarction before age 50 in males or 60 in females). Lipoprotein(a) was analysed both as a binary variable (>125 vs. <125 nmol/L) and as a continuous variable (per 10 nmol/L increase, to enhance interpretability). Figures illustrating the association between continuous Lp(a) levels and CAD outcomes were generated using GraphPad Prism (version 10.4.1), displaying the univariable relationship. However, the corresponding ORs and P-values shown in the figures are derived from multivariable models described above.

To examine whether the relationship between Lp(a) group (>125 vs. <125 nmol/L), exercise status, and CAD differed, we first assessed whether Lp(a) confounded the association between exercise group (lifelong athletes vs. controls) and CAD by comparing unadjusted and Lp(a)-adjusted logistic regression models. Minimal changes in ORs suggested no confounding. Next, an interaction term between Lp(a) group (>125 vs. <125 nmol/L) and exercise group (lifelong athletes, late-onset athletes, and controls) was added to logistic regression models adjusted for Lp(a) and other CV risk factors. A two-sided P-value < 0.05 was considered statistically significant.

Results

Demographics and exercise characteristics

558 participants were included, comprising 482 individuals with low Lp(a) (<125 nmol/L) and 76 with elevated Lp(a) (>125 nmol/L).

There were no significant differences between Lp(a) groups in age, BMI, resting heart rate, triglycerides, HbA1c, family history of CAD, weekly exercise volume, cumulative years of endurance training, MET-min/week, and VO₂peak ($P > 0.05$), see [Table 1](#).

Association between elevated lipoprotein(a) levels and cardiovascular risk factors

Participants with elevated Lp(a) levels had modestly higher systolic and diastolic blood pressure compared with those with lower Lp(a) levels [126.5 (117.0–137.8) vs. 122.0 (115.0–130.0)] mmHg, $P = 0.038$ and 78.0 (70.0–85.0) vs. 75.5 (70.0–80.0) mmHg, $P = 0.030$]. Moreover, significant differences in lipid profiles were observed. Individuals in the high Lp(a) group had higher levels of total cholesterol [207.6 (195.0–231.0) vs. 191.0 (169.0–212.0) mg/dL, $P < 0.001$], LDL cholesterol [138.0 (117.0–160.0) vs. 123.0 (104.0–142.0) mg/dL, $P < 0.001$], and HDL cholesterol [64.2 (56.1–77.5) vs. 62.0 (53.0–71.6) mg/dL, $P = 0.039$], see [Table 1](#).

Elevated lipoprotein(a) > 125 nmol/L and coronary artery disease

Chi-square tests demonstrated a significant association between Lp(a) levels and the presence of CAD ([Figure 1](#) and [Supplementary material](#)

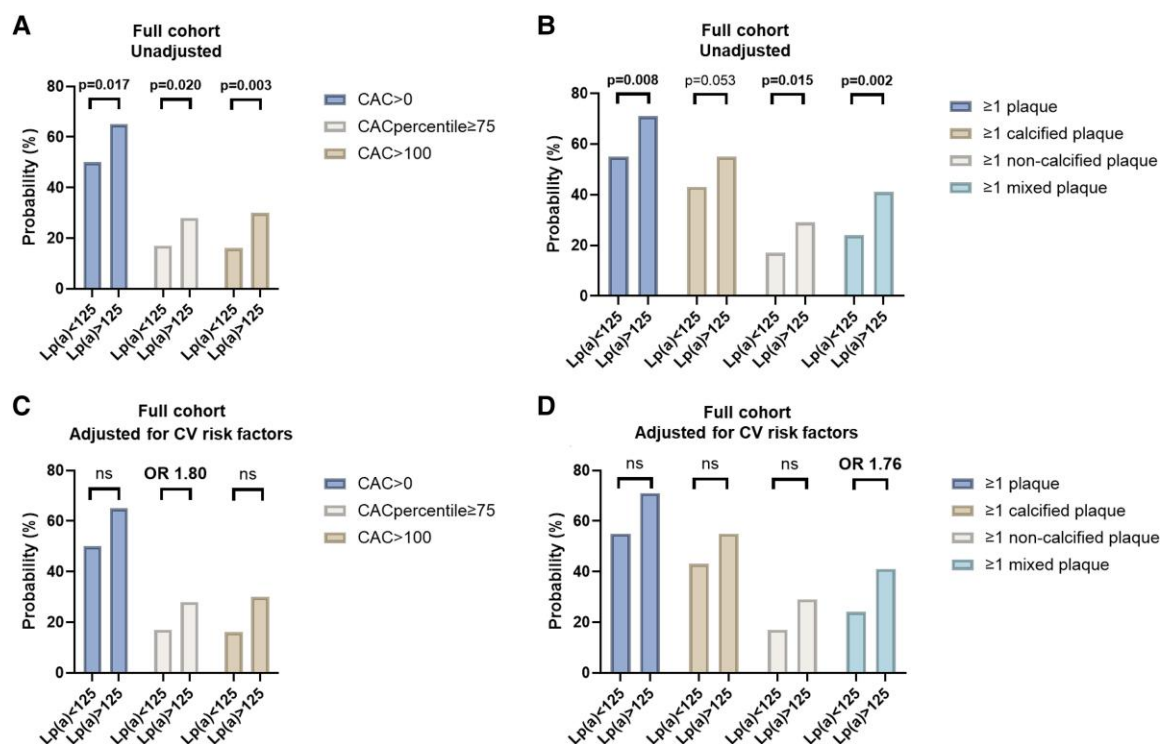


Figure 1 The association between lipoprotein(a) and coronary artery disease. (A and B) Unadjusted associations in the full cohort between lipoprotein(a) and (A) coronary artery calcification and (B) coronary plaques, assessed using χ^2 tests. (C and D) Associations in the full cohort between lipoprotein(a) and (C) coronary artery calcification and (D) coronary plaques, analysed using multiple logistic regression models, adjusted for age, LDL cholesterol, HDL cholesterol, HbA1c, systolic and diastolic blood pressure, body mass index, family history of coronary artery disease, and MET-min/week. P-values for each outcome were as follows: CAC > 0 ($P = 0.092$); CAC percentile ≥ 75 ($P = 0.049$); CAC > 100 ($P = 0.058$); ≥ 1 plaque ($P = 0.057$); ≥ 1 calcified plaque ($P = 0.181$); ≥ 1 non-calcified plaque ($P = 0.104$); ≥ 1 mixed plaque ($P = 0.046$). Odds ratios are shown only when statistically significant.

online, Table S1). In multiple logistic regression models adjusting for age, LDL cholesterol, HDL cholesterol, HbA1c, systolic and diastolic blood pressure, BMI, family history of CAD, and physical activity (MET-min/week), elevated Lp(a) (>125 nmol/L) was significantly associated with several markers of coronary atherosclerosis.

Specifically, the prevalence of an age-specific CAC percentile ≥ 75 was significantly higher in the high Lp(a) group compared with the low Lp(a) group [27.6 vs. 16.6%, OR = 1.80 (95% CI: 1.00–3.24), $P = 0.049$]. Similarly, the presence of mixed plaques was more common in the high Lp(a) group [40.8 vs. 23.9%, OR = 1.76 (95% CI: 1.01–3.07), $P = 0.046$]. While similar trends were observed for CAC > 0 (64.5 vs. 49.8%), CAC > 100 (30.3 vs. 16.2%), ≥ 1 plaque (71.1 vs. 54.8%), ≥ 1 calcified plaque (55.3 vs. 43.4%) and ≥ 1 non-calcified plaque (28.9 vs. 17.2%), these associations did not reach statistical significance (all $P > 0.05$; Table 2 and Figure 1). Subgroup analyses of baseline characteristics, CAD prevalence, and the association with Lp(a) across the three predefined age groups (young, middle-aged, and old) are presented in Supplementary material online, Tables S2–S4. Elevated Lp(a) was similarly associated with CAD in the young and middle-aged subgroups. In the young cohort, a significant association was observed with the presence of ≥ 1 mixed plaque. In the middle-aged cohort, significant associations were found for CAC > 100 and the presence of ≥ 1 calcified plaque. In contrast, no significant associations or observable trends between Lp(a) and CAD were present in the old cohort.

Association between continuous lipoprotein(a) and coronary artery disease

In multiple logistic regression analyses, adjusting for traditional CV risk factors, Lp(a) values were scaled per 10 nmol/L increments to allow the ORs to represent the change in odds of CAD associated with each 10 nmol/L increase in Lp(a). Significant associations were observed between higher Lp(a) and age-specific CAC percentile ≥ 75 [OR = 1.04 (95% CI: 1.01–1.07), $P = 0.014$], CAC > 100 [OR = 1.03 (95% CI: 1.00–1.06), $P = 0.045$], and ≥ 1 mixed or non-calcified plaque [OR = 1.03 (95% CI: 1.00–1.06), $P = 0.029$], see Table 2 and Figure 2.

All significant predictors from the multiple logistic regression models for each different subclinical CAD marker are presented in Supplementary material online, Table S5.

Lipoprotein(a) across exercise groups

Lp(a) concentrations did not differ between lifelong endurance athletes, late-onset athletes, and healthy controls [geometric mean (95% CI): 23.5 (19.9–27.7), 23.1 (19.5–27.3), and 25.7 (21.5–30.6) nmol/L, respectively; $P = 0.586$]. Similarly, the proportion of individuals with elevated Lp(a) >125 nmol/L was comparable across exercise groups (12.0, 14.1, and 14.8%, respectively; $P = 0.724$), see Table 3.

Unadjusted and Lp(a)-adjusted ORs comparing lifelong athletes and healthy controls showed minimal differences across CAD measures: CAC > 0 [OR = 1.60 (1.06–2.41) vs. 1.63 (1.08–2.47)], CAC

Table 2 The association between lipoprotein(a) and coronary artery disease, adjusted for multiple traditional cardiovascular risk factors

	Lp(a) < 125 (n = 482)	Lp(a) > 125 (n = 76)	OR (95% CI)	P-value
Full cohort (n = 558)				
CAC > 0	240 (49.8%)	49 (64.5%)	1.61 (0.93–2.81)	0.092
CAC percentile ≥ 75	80 (16.6%)	21 (27.6%)	1.80 (1.00–3.24)	0.049
CAC > 100	78 (16.2%)	23 (30.3%)	1.80 (0.98–3.31)	0.058
≥1 plaque	264 (54.8%)	54 (71.1%)	1.76 (0.98–3.14)	0.057
≥1 calcified plaque	209 (43.4%)	42 (55.3%)	1.44 (0.84–2.47)	0.181
≥1 non-calcified plaque	83 (17.2%)	22 (28.9%)	1.64 (0.90–2.98)	0.104
≥1 mixed plaque	115 (23.9%)	31 (40.8%)	1.76 (1.01–3.07)	0.046
OR (95% CI interval) per 10 nmol/L increase in continuously measured Lp(a)				
CAC > 0			1.02 (0.99–1.05)	0.185
CAC percentile ≥ 75			1.04 (1.01–1.07)	0.014
CAC > 100			1.03 (1.00–1.06)	0.045
≥1 plaque			1.02 (0.99–1.05)	0.199
≥1 calcified plaque			1.01 (0.99–1.04)	0.301
≥1 non-calcified plaque			1.02 (0.99–1.05)	0.236
≥1 mixed plaque			1.03 (1.00–1.05)	0.059
≥1 mixed or non-calcified			1.03 (1.00–1.06)	0.029

Bold values indicated plaque significance.
Multiple logistic regression analysis adjusted for age, LDL cholesterol, HDL cholesterol, HbA1c, systolic and diastolic blood pressure, BMI, family history of CAD, and MET-min/week. Data are presented as n (%), with percentages relative to the [Lp(a)] group. Odds ratios are reported with 95% CIs. Lipoprotein(a) levels are expressed in nmol/L. In the upper part of the table, Lp(a) is included in the model as a binary variable (<125 vs. >125 nmol/L). In the lower part, Lp(a) is modelled as a continuous variable, scaled per 10 nmol/L increase, to reflect the change in probability per 10 nmol/L rise in Lp(a) concentration.

percentile ≥ 75 [1.54 (0.91–2.60) vs. 1.58 (0.93–2.68)], CAC > 100 [1.73 (1.01–2.95) vs. 1.79 (1.04–3.08)], and ≥1 plaque [1.73 (1.14–2.62) vs. 1.78 (1.17–2.70)], see [Table 3](#).
Additionally, no significant interaction effects between Lp(a) group (>125 vs. <125 nmol/L) and exercise group were observed when added to the multiple logistic regression model alongside Lp(a) and other CV risk factors to predict various CAD measures ($P > 0.05$), see [Table 4](#).

Discussion

In this large, well-characterized cohort of ageing male endurance athletes and healthy controls with a low CV risk profile, we observed a significant association between elevated Lp(a) levels and subclinical CAD ([Graphical Abstract](#)). Specifically, high Lp(a) concentrations (>125 nmol/L) were independently associated with an age-specific CAC percentile ≥ 75 and the presence of at least one mixed plaque. Continuously measured Lp(a) was even independently associated with CAC > 100, a threshold known to predict increased CV event risk.¹⁴ While the ORs for continuously measured Lp(a) were modest (e.g. 1.03 per 10 nmol/L increase for CAC > 100, corresponding to 3% higher odds per 10 nmol/L increase), this reflects the continuous nature of the relationship across the population, where lower Lp(a) values contribute little additional risk and the effect becomes more pronounced at higher concentrations. This supports the use of the commonly applied clinical cutoff of >125 nmol/L to identify individuals with substantially elevated CAD risk. These findings were independent of traditional CV risk

factors and exercise characteristics, underscoring the potential role of Lp(a) as an adjunctive marker for CAD risk stratification in physically active populations. However, Lp(a) did not appear to explain the higher CAD prevalence observed in lifelong endurance athletes compared with controls.

Lipoprotein(a) and subclinical coronary artery disease in athletic populations

Lipoprotein(a) is a well-established, genetically determined, and independent risk factor for atherosclerotic CV disease in the general population. Its pro-atherogenic, pro-inflammatory, and pro-thrombotic properties are well described, and its causal relationship with CAD has been supported by large-scale Mendelian randomization studies.^{7–9,15} However, the relevance of Lp(a) in physically active individuals, particularly Masters athletes, who typically exhibit favourable cardio-metabolic profiles, remains largely unexplored. Our study extends the literature by demonstrating that Lp(a) retains its predictive value in an ostensibly healthy and physically active cohort. This suggests that Lp(a), unlike many traditional risk factors, may not be mitigated by physical fitness or a favourable lifestyle alone.
Current American Heart Association and European Society of Cardiology consensus documents recommend a CV assessment in Masters athletes, typically in those over 35 years of age, based on clinical evaluation and traditional risk scores such as SCORE2. These tools are designed to identify individuals at elevated risk for CV events and to guide decisions regarding further diagnostic testing, including coronary imaging. However, they are heavily reliant on modifiable risk factors

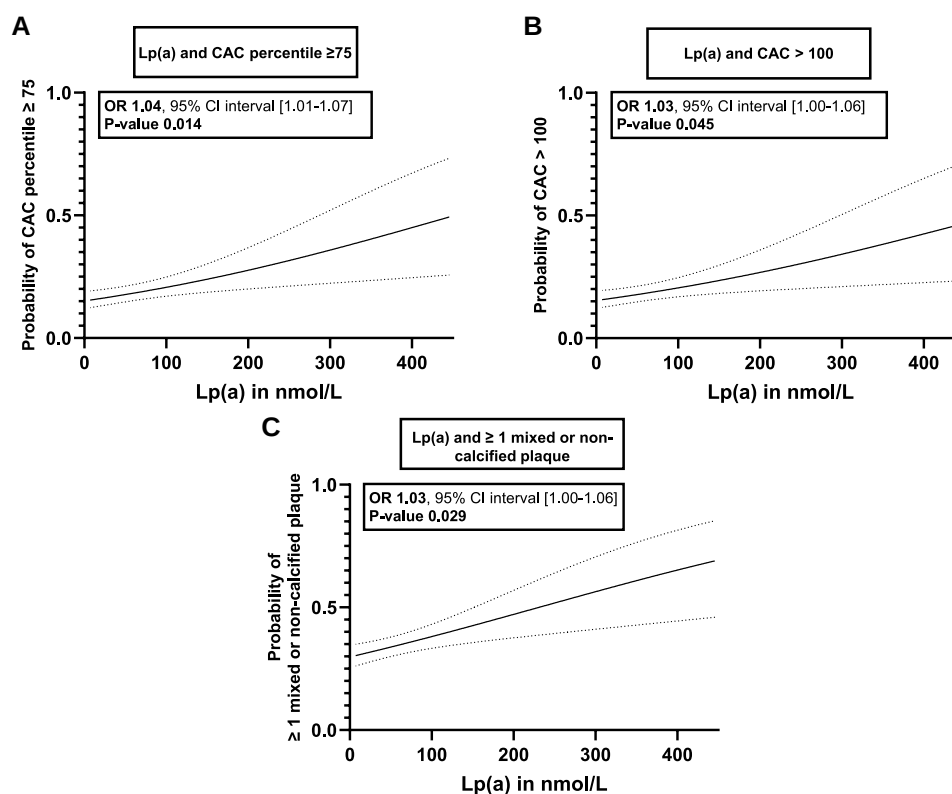


Figure 2 The association between continuously measured lipoprotein(a) and coronary artery disease. Logistic regression plots show the association between continuous lipoprotein(a) levels and subclinical coronary artery disease. (A) Age-adjusted coronary artery calcification percentile ≥ 75 ; (B) coronary artery calcification score > 100 ; (C) presence of ≥ 1 mixed or non-calcified plaque. The plotted associations reflect univariable logistic regression, while the odds ratios and 95% confidence intervals shown are derived from the multivariable-adjusted models (adjusted for age, LDL cholesterol, HDL cholesterol, HbA1c, systolic and diastolic blood pressure, body mass index, family history of coronary artery disease, and MET-min/week). The magnitude of odds ratios were similar in univariable and multivariable adjusted models, though *P*-values were more strongly significant in the univariable analysis. The lipoprotein(a) concentration was modelled as a continuous variable, divided by 10, such that the odds ratios represent the change in odds per 10 nmol/L increase in lipoprotein(a). For example, an odds ratio of 1.04 corresponds to a 4% higher odds of the outcome per 10 nmol/L increase in lipoprotein(a).

Table 3 Lipoprotein(a) across exercise groups

	Lifelong athletes (<i>n</i> = 191)	Late-onset athletes (<i>n</i> = 191)	Healthy controls (<i>n</i> = 176)	<i>P</i> -value
Lp(a)—nmol/L	23.5 (19.9–27.7)	23.1 (19.5–27.3)	25.7 (21.5–30.6)	0.586
Lp(a) > 125 nmol/L— <i>n</i> (%)	23 (12.0)	27 (14.1)	26 (14.8)	0.724
Lifelong athletes vs. healthy controls				
	OR unadjusted	<i>P</i> -value	OR adjusted for Lp(a) group	<i>P</i> -value
CAC > 0	1.60 (1.06–2.41)	0.026	1.63 (1.08–2.47)	0.021
CAC percentile ≥ 75	1.54 (0.91–2.60)	0.111	1.58 (0.93–2.68)	0.093
CAC > 100	1.73 (1.01–2.95)	0.046	1.79 (1.04–3.08)	0.035
≥ 1 plaque	1.73 (1.14–2.62)	0.010	1.78 (1.17–2.70)	0.007

Bold values indicated statistical significance.

Lipoprotein(a) values are presented as geometric means with 95% CIs. The proportion of individuals with elevated Lp(a) within different exercise groups is presented. Odds ratios from logistic regression were used to assess the presence of CAD by comparing lifelong endurance athletes with healthy controls, both before and after adjustment for Lp(a) group (> 125 vs. < 125 nmol/L).

Table 4 Interaction term of lipoprotein(a) group and exercise group

	P-value of interaction term Lp(a) group × exercise group
CAC > 0	0.453
CAC percentile ≥ 75	0.354
CAC > 100	0.876
≥1 plaque	0.661
≥1 calcified plaque	0.264
≥1 non-calcified plaque	0.454
≥1 mixed plaque	0.338

The P-value for the interaction term between lipoprotein(a) (>125 vs. <125 nmol/L) and exercise group (lifelong athlete, late-onset athlete, or control) is presented for each CAD measure. Interaction terms were included in the multiple logistic regression model, adjusting for other CV risk factors.

(e.g. hypertension, dyslipidaemia, diabetes, smoking), and may be less sensitive in populations with low conventional risk, such as Masters athletes.^{1,4,16,17} Our findings demonstrate that these conventional risk models may not adequately capture CV risk in a highly trained population. In our cohort, no participants would have qualified for CCTA based on traditional screening criteria, yet several individuals were found to have important CAD burden. These results highlight a potential blind spot in the current risk assessment paradigm and suggest that Lp(a), as a relatively stable, genetically encoded biomarker, may help uncover hidden CV risk in this context.

Moreover, the association between Lp(a) and the presence of mixed and non-calcified plaques in our study is particularly noteworthy. Mixed and non-calcified plaques are considered to be more vulnerable than calcified plaques and are more strongly associated with acute coronary events.⁶ These findings are consistent with prior studies in general populations, including longitudinal imaging studies that linked elevated Lp(a) to coronary plaque progression, higher non-calcified plaque burden, and increased coronary inflammation.¹⁸

Clinical implications

Our findings may have important implications for CV risk stratification in Masters athletes and other physically active populations. While physical fitness provides numerous CV benefits, it does not uniformly protect against coronary atherosclerosis. Indeed, ageing athletes may develop distinct patterns of CAD, with higher calcified plaque burden and a higher prevalence of subclinical disease than their sedentary peers.²⁻⁴ The addition of Lp(a) to screening protocols could help identify those individuals who, despite being fit and asymptomatic, harbour clinically relevant coronary lesions.¹⁹

Coronary computed tomography angiography is an effective, non-invasive tool for detecting and quantifying coronary atherosclerotic burden.²⁰⁻²² Across multiple large-scale cohort studies, CAC burden assessed by CCTA independently predicts future CV events.^{23,24} Coronary artery calcification >100 indicates a substantially increased risk for major CV events.¹⁴ In younger populations, age-specific CAC percentiles enable detection of disproportionate CAC burden relative to peers.²⁵ In our study, Lp(a) was significantly associated with CAC > 100 and age-specific CAC percentile ≥ 75, both recognized thresholds in primary prevention guidelines for statin initiation, supporting its role in guiding imaging decisions and early risk stratification.^{14,26} By contrast, Sung et al.²⁷ found no

association between elevated Lp(a) and incident or progressive CAC over four years in the general population. However, their analysis focused exclusively on CAC, potentially missing mixed and non-calcified plaques, which we also assessed and found to be consistently associated with Lp(a). While both populations typically exhibit relatively low Lp(a) levels,⁹ differences in study populations may also contribute, as their Southeast Asian cohort included more individuals with traditional risk factors (e.g. smoking, diabetes mellitus), whereas our West-European cohort was low-risk and physically active. It is possible that, in our low-risk cohort with minimal confounding from traditional CV risk factors, the independent relationship between Lp(a) and subclinical CAD becomes more apparent.

Emerging evidence suggests that the long-term implications of subclinical CAD in ageing athletes are comparable to those observed in less active populations. High physical activity does not appear to mitigate the adverse effects of elevated CAC. Gerber et al.²⁸ found that elevated CAC in athletes was still linked to increased CV risk despite high fitness. Similarly, earlier findings of the Cooper Center Longitudinal Study showed that while higher fitness reduced CV risk at each CAC level, athletes with high CAC remained at greater risk of events compared with sedentary individuals without CAC.²⁹ Recent findings from the same cohort further refined this understanding by demonstrating that elevated CAC was even similarly associated with clinical CAD events (acute myocardial infarction and revascularization) across all levels of physical activity. Individuals with CAC 1–99 had a two-fold, and those with CAC > 100 a four-fold increased risk of acute myocardial infarction, compared with CAC 0.³⁰ These findings reinforce that ageing endurance athletes with CAC > 100 and/or age-specific CAC percentile ≥ 75, particularly those with elevated Lp(a),¹⁸ may benefit from risk-modifying therapies as recommended in the general population.^{14,26} Given that Lp(a) remained predictive of elevated CAC burden, even in our cohort with a low traditional CV risk profile, and that one-time measurement is already advised in the general population,⁸ Lp(a) testing should be strongly considered in asymptomatic ageing athletes.

Current Lp(a) management strategies emphasize lifestyle optimization, however evidence indicates that lifestyle and physical activity has little to no effect on lowering Lp(a) levels.⁸ Most studies have found no association between exercise and Lp(a),^{8,31} and in our cohort, Lp(a) concentrations did not differ between athletes and controls. Nevertheless, regular moderate exercise remains an important recommendation during patient counselling due to its well-established benefits on overall CV health.⁸ In the presence of elevated Lp(a), early intensified management of other modifiable risk factors, such as LDL cholesterol reduction and blood pressure control, is essential to effectively lower the global CV risk.⁸ While therapies like statins do not lower Lp(a), upcoming therapies—such as proprotein convertase subtilisin/kexin Type 9 inhibitors and antisense oligonucleotides targeting apolipoprotein(a)—may offer effective means of lowering Lp(a).⁷ The value of measuring Lp(a) will be even greater if treatments targeted at Lp(a) prove effective at reducing CV events.

Pathophysiological considerations in ageing athletes

The mechanisms underlying the higher prevalence of CAD in ageing endurance athletes compared with healthy controls remain incompletely understood.^{32,33} While traditional risk factors play a role, emerging evidence suggests that non-traditional contributors, both physiological and environmental, may be particularly relevant in this population.^{32,33} In our cohort, Lp(a) levels and the proportion of individuals with elevated Lp(a) did not differ significantly between lifelong athletes,

late-onset athletes, and controls. Moreover, adjustment for Lp(a) did not attenuate the higher prevalence of CAD observed in lifelong athletes compared with healthy controls, suggesting that elevated Lp(a) does not account for this difference. Furthermore, no significant interaction effects between Lp(a) and exercise group were found when added to the multiple logistic regression model predicting CAD outcomes, indicating that the relationship between Lp(a) and CAD is similar across exercise groups.

Although Lp(a) was not a significant predictor of CAD in the athletic MARC-2 study, that cohort included individuals with traditional risk factors (e.g. hypertension, diabetes, smoking), potentially confounding results.^{3,32} Our study, by excluding such individuals, may help to provide a clearer picture of the independent relationship between Lp(a) and subclinical atherosclerosis.

Studies by Berge *et al.*³² have identified several non-traditional risk factors for coronary calcification in endurance athletes, including life-long training load (MET-h/week), dietary patterns, and elevated serum phosphate levels. High phosphate concentrations are thought to promote vascular calcification, particularly when combined with repetitive mechanical stress from endurance exercise.^{32–34} Additionally, dietary composition appears relevant: higher dietary fat intake, particularly monounsaturated fats as seen in the Mediterranean diet, has been inversely associated with CAC.^{32,35} These findings support a broader view of CAD pathogenesis in athletes, in which genetic, mechanical, metabolic, and lifestyle-related factors interact in complex ways.

Strengths and limitations

This study benefits from a large, well-characterized cohort of physically active men without diagnosed CV risk factors, allowing for the evaluation of Lp(a) as an independent marker of subclinical CAD. High-resolution CCTA enabled precise assessment of plaque burden, while Lp(a) was measured using a validated assay calibrated in nmol/L and minimally affected by apolipoprotein(a) isoform size.

Several limitations merit consideration. Although the Master@Heart study is prospective, the current analysis is cross-sectional, limiting causal inference. The inclusion of only white Caucasian men restricts generalizability to women and other ethnic groups. Undiagnosed conditions such as elevated blood pressure, dyslipidaemia, or (mild) diabetes mellitus may have been present, and lifetime training load was self-reported, introducing potential recall bias. Despite extensive phenotyping, residual confounding from unmeasured factors, such as dietary habits or genetic predisposition, cannot be excluded. There was only one measurement of Lp(a), which limits our ability to assess its temporal stability. On the one hand, intensive physical activity may induce acute phase-like transient changes in Lp(a) levels. However, findings on this phenomenon have been inconsistent in the literature.^{36–38} On the other hand, recent research suggests that intermediate Lp(a) concentrations can fluctuate over time, potentially affecting the interpretation of its association with coronary atherosclerosis.³⁹ Finally, the long-term prognostic significance of Lp(a)-associated subclinical CAD in our cohort remains to be determined.

Future directions

Prospective longitudinal follow-up of this cohort will be essential to assess the prognostic significance of elevated Lp(a) and subclinical CAD in endurance athletes. Future work should explore the interaction of Lp(a) with polygenic risk scores and other non-traditional biomarkers to enhance personalized risk prediction. Recent findings by Manikpurage *et al.*⁴⁰ showed that individuals with both elevated Lp(a) and high CAD

polygenic risk scores may face a markedly increased risk of CV events, highlighting the potential for integrated, precision-based approaches. Further studies should also include women and ethnically diverse populations to improve generalizability and assess whether upcoming Lp(a)-lowering therapies may reduce risk in high-Lp(a) individuals.

Conclusions

Elevated Lp(a) levels, both at the clinically relevant threshold (>125 nmol/L) and as a continuous variable, are independently associated with subclinical CAD in ageing endurance athletes and healthy controls, even in the absence of traditional CV risk factors. Lipoprotein(a) does not explain the higher CAD prevalence observed in lifelong endurance athletes compared with controls, but may enhance risk-stratification in this low-risk population.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

R.P. led data analysis and drafted the manuscript. R.D.B. supported data collection. J.D.P., C.D., Y.B., and B.D. assisted with data. S.D. and O.G. conducted data analysis. L.B. conducted statistical analysis. C.M.V.D.H. and P.L.V.H. supported data and analysis. L.H. contributed to study design, data, and supervision. T.K., P.S., and T.R. contributed to supervision. R.W., H.H., A.L.G., and G.C. led study design, investigation, supervision, and funding. G.C. also supported the original draft. All authors reviewed the manuscript and gave approval.

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Ethical approval

The research protocol was approved by the ethics committee of KU Leuven (S61336). All participants gave written informed consent.

Conflict of interest: none declared.

Data availability

The data is available only after reasonable request.

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