Association between lipoprotein(a) (Lp(a)) levels and Lp(a) genetic variants with coronary artery calcification

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Abstract

Background: To examine the association between lipoprotein(a) (Lp(a)) levels, \textit{LPA} (rs10455872 and rs3798220) and \textit{IL1F9} (rs13415097) single nucleotide polymorphisms (SNPs) with coronary artery calcification (CAC), an important predictor for coronary artery disease (CAD).

Methods: We used data from 3799 (mean age ± SD: 59.0 ± 7.7 years, 47.1% men) Heinz Nixdorf Recall study participants. We applied linear regression models to explore the relation between the log-transformed Lp(a) levels and \textit{LPA} and \textit{IL1F9} SNPs with log \( \text{e} \) (CAC + 1). The association between the SNPs and log-transformed Lp(a) levels was further assessed using linear regression. The models were adjusted for age and sex (Model 1) and additionally for Lp(a) levels (Model 2).

Results: We observed a statistically significant association between log-transformed Lp(a) levels and CAC (Model 1: beta per log-unit increase in Lp(a) levels = 0.11; 95% confidence interval [95% CI] [0.04; 0.18], \( p = 0.002 \)). Furthermore, the \textit{LPA} SNP rs10455872 showed a statistically significant association with CAC (Model 1: beta per allele = 0.37 [0.14; 0.61], \( p = 0.002 \)). The association between rs10455872 and CAC was attenuated after adjustment for Lp(a) levels (Model 2: beta per allele = 0.26 [-0.01; 0.53], \( p = 0.06 \)). Both \textit{LPA} SNPs also showed a statistically significant association with Lp(a) levels (Model 1: beta rs10455872 per allele: 1.56 [1.46; 1.65], \( p < 0.0001 \) and beta rs3798220 per allele: 1.51 [1.33; 1.69], \( p < 0.0001 \)). The Mendelian randomization analysis showed that Lp(a) is a causal risk factor for CAC (estimate per log-unit increase in Lp(a) levels (95% CI), \( p = 0.27 \) [0.11; 0.44], \( p = 0.001 \)). The \textit{IL1F9} SNP did not show any statistically significant association with Lp(a) levels or with CAC.

Conclusions: We provide evidence for the association of \textit{LPA} rs10455872 with higher levels of Lp(a) and CAC in our study. The results of our study suggest that rs10455872, mediated by Lp(a) levels, might play a role in promoting the development of atherosclerosis leading to cardiovascular disease events.

Keywords: Lp(a), LPA genetic variants, Coronary artery calcification

Background

Lipoprotein(a) (Lp(a)) is a complex particle and has similarities with apolipoprotein (apo) (a) and apoB linked by a disulfide bond [1]. The role of Lp(a) is well established for the risk of coronary artery disease (CAD) [2, 3]. Genome-wide association studies (GWAS) have identified two single nucleotide polymorphisms (SNPs)
at the Lp(a) locus (LPA) on chromosome 6q26–27 (rs3798220 and rs10455872) that were strongly and independently related to Lp(a) levels and with the risk of CAD [3–7]. Coronary artery calcification (CAC) is an important predictor of CAD, and its extent is directly related to the atherosclerotic plaque burden. Quantification of CAC has been shown to allow better risk prediction of future cardiovascular disease (CVD) events [8, 9]. Furthermore, studies have examined the association of Lp(a) with CAC and have shown conflicting results [10–14]. Kullo et al. and Guerra et al. showed no relationship between Lp(a) and CAC score [13, 14]. However, Erbel et al., Greif et al. and Alonso et al. showed a positive relationship between Lp(a) and CAC score [10–12]. In a GWAS, the LPA rs10455872 SNP was associated with aortic valve calcification (AVC) [15]. In this study, two other SNPs that are in high linkage disequilibrium (LD) near the proinflammatory gene (IL1F9) (rs17659543 and rs13415097) also achieved GWA significance with mitral annular calcification (MVC). Both AVC and MVC have been associated with the risk of CVD [16–18].

Understanding the effects of Lp(a) as well as the SNPs in the LPA and IL1F9 genes on CAC might provide insight into the mechanisms by which they cause CAD. Hence, the aim of our study was to examine the association between the LPA and IL1F9 SNPs with CAC in relation to the Lp(a) levels by using the data of the population-based Heinz Nixdorf Recall study participants.

Measurement of Lp(a) levels
After blood collection, the samples were immediately sent to our central laboratory and centrifuged, and the Lp(a) concentration (mg/dL) was analyzed in serum. For the remainder of the manuscript, Lp(a) is used instead of Lp(a) levels. Lp(a) was quantified using a particle-enhanced immunonephelometric method using the BN II system from Siemens Healthcare (Eschborn, Germany).

Assessment of coronary artery calcification
As described previously, baseline CAC was assessed by a nonenhanced electron-beam scan (C-100 or C-150 scanner; GE Imatron, San Francisco, CA, USA) [19]. Furthermore, prospective ECG triggering was done at 80% of the RR interval, and at an image acquisition time of 100 ms, contiguous 3 mm thick slices from the pulmonary bifurcation to the apex of the heart were obtained in both scans [24, 25]. Quantification of CAC score was done using the method suggested by Agatston et al. [26]. The analyses were performed using a Virtuoso workstation (Siemens Medical Solutions, Forchheim, Germany). We further addressed the marked right-skewed distribution of CAC by using the loge transformation of CAC score plus 1, as previously suggested [27–30].

Assessment of risk factors
The risk factors were recorded at baseline. Smoking behavior (smokers (defined as current or past smokers) and nonsmoker) was assessed in detail [24]. Body mass index (BMI) was calculated as weight divided by height square (kg/m²). Current and regular use of medication i.e., antihypertensive or lipid-lowering medication, was recorded in a standardized assessment of medication. The resting blood pressure was measured thrice, with the participants seated by using an automated oscillometric blood pressure device (Omron, HEM-705CP-E). The mean of the second and third values was calculated and used in this study [31]. Standardized enzymatic methods were used to determine serum low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride values (ADVIA 1650, Siemens Medical Solutions, Erlangen, Germany). Diabetes was defined as meeting any of following 4 criteria: (1) participants reported a history of clinically diagnosed diabetes, (2) participants took glucose-lowering drugs, (3) participants had fasting glucose levels of greater than 125 mg/dL, or (4) participants had nonfasting glucose levels of 200 mg/dL or greater [30].

Genotyping
The participants (n = 4331) were genotyped using Illumina GWAS chips (Omni1, OmniExpress, OmniExpress1, HumanCoreExome v1.0 and v1.1) [25, 32]. The 1000 Genomes Project (release October 2014) was used
We performed power calculation using QUANTO Version 1.2.4 (http://hydra.usc.edu/gxe) considering a MAF of ≥5% and \( \alpha_{BF} = 0.0167 \) (two-sided). For a sample of 2116 participants (those with CAC > 0), the comparison-wise power estimate was 97% (or 67%) assuming a standard normally distributed quantitative trait locus and a standardized effect size of 0.3 (or 0.2) in units of standard deviations (SD) for each risk allele under an additive mode of inheritance without dominance effects. Thus, our study was powered to detect a relatively strong effect size of quantitative CAC predisposing variants when controlling for multiple testing.

Since rs10455872 has been associated with AVC [15], we performed sensitivity analyses by excluding the participants with the presence of AVC (\( N = 464 \)) at baseline in the analyses testing the association between rs10455872 and CAC.

Continuous data are presented as the mean ± SD or median (first quartile: Q1, third quartile: Q3) for skewed data. Accordingly, tests for group differences in the continuous parameters are performed using Student’s \( t \) test or the Mann-Whitney \( U \) test. Count data are presented as frequency and percentage, and the group differences are evaluated by using the \( \chi^2 \) or Fisher exact test. Statistical analyses were performed using SAS v.9.4 and PLINK v.19 (https://www.cog-genomics.org/plink2) [34].

Results

Study characteristics

The basic characteristics of the Heinz Nixdorf Recall study participants are shown in Table 1. In our study, 3799 and 3639 participants had measurements of Lp(a) and CAC, respectively. Differences in LDL cholesterol, HDL cholesterol, total cholesterol and use of lipid-lowering medication were observed in the Lp(a) stratified groups (Table 1). Figure 1 shows the distribution of log-transformed Lp(a) according to the genotypes for all three SNPs. For rs10455872 and rs3798220, due to the smaller numbers of participants having both risk alleles (BB), we combined the BB genotypes with the heterozygous genotype (AB). With every increase in the risk allele for rs10455872 (median (Q1; Q3): AA: 1.66 (1.57; 2.74) and AB or BB: 3.84 (3.58; 4.15)) and rs3798220 (AA: 1.66 (1.57; 3.09) and AB or BB: 4.46 (3.73; 4.71)), the log-transformed Lp(a) was increased. However, for rs13415097, we did not find any impact of genotypes on the levels of Lp(a). Supplementary Figure 1 A and B additionally show the distribution of Lp(a) by genotype for both LPA SNPs. The genotypes for rs10455872 (Supplementary Figure 1A) show better separation of Lp(a) compared to the genotypes for rs3798220 (Supplementary Figure 1B).

Figure 2 shows the distribution of the genotypes for the three SNPs with CAC. For both LPA SNPs, with
every increase in the risk allele, the CAC score (Agatston) also increased (median (Q1; Q3): rs10455872_AA: 9.0 (0; 102.9) and rs10455872_AB or BB: 17.65 (0; 181.7) and (rs3798220_AA: 10.6 (0; 106.5) and rs3798220_AB or BB: 24.2 (0; 129.7)). However, for rs13415097, we did not find any impact of genotypes on the CAC score. Furthermore, the following observations were made in Lp(a) strata (Supplementary Figure 2 A and B). For rs10455872, the Lp(a) < 54.3 mg/dL stratum had a median CAC score (Agatston) of 9.0 (0; 101.3) for AA and 18.1 (0; 165.5) for AB or BB (Supplementary Figure 2A). Similarly, the Lp(a) ≥ 54.3 mg/dL stratum had a median CAC score (Agatston) of 9.3 (0; 126.9) for AA and 13.9 (0; 203.7) for AB or BB (Supplementary Figure 2B). For rs3798220, the Lp(a) < 54.3 mg/dL stratum had a median CAC score (Agatston) of 10.8 (0; 105.2) for AA and 4.6 (1; 66.3) for AB or BB (Supplementary Figure 2A). Similarly, the Lp(a) ≥ 54.3 mg/dL stratum had a median CAC score (Agatston) of 8.8 (0; 169.9) for AA and 39.3 (0; 164.5) for AB or BB (Supplementary Figure 2B).

### Table 1 Basic characteristics of the Heinz Nixdorf Recall study participants

|                              | Unstratified (n = 3799) | Lp(a) < 54.3 mg/dL (n = 3418) | Lp(a) ≥ 54.3 mg/dL (n = 381) | p c |
|------------------------------|-------------------------|-------------------------------|-------------------------------|-----|
| Males N (%)                  | 1788 (47.1)             | 1619 (47.4)                   | 169 (44.4)                    | 0.28|
| Age (years) a                | 59.0 ± 7.7              | 59.0 ± 7.7                    | 59.3 ± 7.8                    | 0.45|
| BMI (kg/m²) a                | 27.8 ± 4.7              | 27.8 ± 4.7                    | 27.4 ± 4.5                    | 0.07|
| Diabetes N (%)               | 452 (11.9)              | 408 (11.9)                    | 44 (11.6)                     | 0.87|
| Antihypertension medication  | 1159 (30.5)             | 1035 (30.3)                   | 124 (32.6)                    | 0.38|
| Diastolic blood pressure (mmHg) a | 81.5 ± 10.7            | 81.5 ± 10.7                   | 81.6 ± 11.0                   | 0.70|
| Systolic blood pressure (mmHg) a | 132.3 ± 20.5           | 132.3 ± 20.6                  | 132.6 ± 20.3                  | 0.63|
| Lipid-lowering medication    | 334 (9.4)               | 286 (9.0)                     | 48 (13.4)                     | 0.01|
| LDL cholesterol (mg/dL) b    | 146.8 ± 36.4            | 145.8 ± 36.3                  | 156.2 ± 35.8                  | < 0.001|
| HDL cholesterol (mg/dL) b    | 59.1 ± 17.3             | 58.8 ± 17.3                   | 61.4 ± 17.0                   | 0.001|
| Total cholesterol (mg/dL) b  | 231.5 ± 39.1            | 230.3 ± 39.0                  | 242.3 ± 38.3                  | < 0.001|
| Triglyceride (mg/dL) b       | 123 (88; 177)           | 123 (89; 176)                 | 124.5 (87.5; 183.0)           | 0.56|
| Smoking                      | 2139 (56.4)             | 1927 (56.4)                   | 212 (55.8)                    | 0.83|
| Lp(a) (mg/dL) a              | 19.9 ± 26.0             | 12.7 ± 12.3                   | 844 ± 28.2                    | NA  |
| Lp(a) (mg/dL) b              | 5.3 (4.8; 23.3)         | 5.3 (4.8; 162)                | 75.2 (625, 983)               | NA  |
| Log (Lp(a)) a                | 2.4 ± 1.0               | 2.2 ± 0.8                     | 4.4 ± 0.3                     | NA  |
| Log (Lp(a)) b                | 1.7 (1.6; 3.1)          | 1.7 (1.6; 2.8)                | 4.3 (4.1; 4.6)                | NA  |
| CAC (Agatston) b             | 108 (0; 107.0)          | 108 (0; 104.9)                | 115 (0; 166.5)                | 0.17|
| Log (CAC + 1) b              | 2.5 (0; 4.7)            | 2.5 (0; 4.7)                  | 2.5 (0; 5.1)                  | 0.17|

BMI Body mass index, LDL Low density lipoprotein, HDL High density lipoprotein. Data are given as numbers (percentages) unless otherwise indicated. *Data are given as the mean ± SD. †Data are given as the median (Q1; Q3). Lp(a) at the 90th percentile is 54.3 mg/dL. The genotypes are as follows: rs10455872: AA = AA; AB or BB = AG + GG, rs3798220: AA = TT; AB or BB = TC + CC, and rs13415097: AA = TT; AB = TC; BB=CC. ‡p are for differences between Lp(a) stratified groups using χ² or Fisher exact test, t test or Mann-Whitney U test. NA Not applicable

Association of genetic variants with coronary artery calcification

In the age- and sex-adjusted analysis, the SNP rs10455872 was statistically significantly associated with CAC (beta per allele = 0.37 [95% CI] [0.14; 0.61], *p* = 0.002) (Table 2). After adjustment for age, sex and Lp(a) levels, the association between the SNP and CAC was
attenuated. The association between rs10455872 and CAC showed borderline statistical significance ($0.26 [-0.01; 0.53]$, $p = 0.06$) (data not shown). SNP rs3798220 did not show any statistically significant association with CAC, although the effect size was high (Table 2). SNP rs13415097 did not show any statistically significant association with CAC (Table 2). The association between rs10455872 and CAC remained significant at a nominal level even after adjusting for risk factors ($0.24 [0.01; 0.48]$, $p = 0.04$) (age, sex, smoking, BMI, HDL cholesterol, LDL cholesterol, triglyceride, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medication and lipid-lowering medication) (data not shown).

Since rs10455872 is associated with AVC, we performed sensitivity analyses by excluding the participants with the presence of AVC at baseline. In the age- and sex-adjusted analysis, the association of rs10455872 with CAC remained significant at the nominal level ($0.30 [0.05; 0.55]$, $p = 0.018$) (data not shown). Further adjustment for Lp(a) attenuated the association ($0.22 [-0.07; 0.51]$, $p = 0.13$) (data not shown).

**Association of Lp(a) with coronary artery calcification**

Table 3 shows the association of Lp(a) with CAC. Log-transformed Lp(a) (beta per log unit increase in Lp(a) = $0.11 [95\% CI] [0.04; 0.18]$, $p = 0.002$) and categories of Lp(a) ($Lp(a) \geq 54.3 \text{mg/dL}$ vs. $Lp(a) < 54.3 \text{mg/dL}$) ($0.23 [0.005; 0.45]$, $p = 0.05$) were statistically significantly associated with CAC in the age- and sex-adjusted analyses. The additional phenotypic variance explained by the addition of log-transformed Lp(a) or Lp(a) categories to the base model (age and sex: $R^2 = 25.3\%$) was 0.2 and 0.1%, respectively. **Supplementary Figure 3** additionally shows the association between the log-transformed Lp(a) and CAC in an unadjusted linear analysis that resulted in an estimate of $0.09 [0.01; 0.17]$, $p = 0.03$, similar to the adjusted analysis (Table 3). The association
between log-transformed Lp(a) and CAC (0.09 [0.02; 0.16], \( p = 0.008 \)) remained statistically significant even after adjusting for risk factors (age, sex, smoking, BMI, HDL cholesterol, LDL cholesterol, triglyceride, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medication and lipid-lowering medication) (data not shown). However, the association between Lp(a) categories and CAC was not statistically significant after adjusting for risk factors (0.18 [−0.05; 0.40], \( p = 0.13 \)) (data not shown). As a sensitivity analysis, we looked at the association between Lp(a) and CAC quintiles of CAC in an unadjusted model (Supplementary Figure 4). Within a given CAC quantile, the value of CAC increases with increasing Lp(a).

**Table 2** Association between LPA and IL1F9 single nucleotide polymorphisms with log \( \text{e} \) (CAC Score+ 1)

| Gene | SNP     | N     | Unstratified Beta [95% CI], \( p \) |
|------|---------|-------|-----------------------------------|
| LPA  | rs10455872 | 3167  | 0.37 [0.14; 0.61], 0.002          |
| LPA  | rs3798220  | 3620  | 0.22 [−0.17; 0.62], 0.26          |
| IL1F9| rs13415097 | 3615  | −0.09 [−0.22; 0.04], 0.19         |

**Table 3** Association between Lp(a) and log \( \text{e} \) (CAC Score+ 1)

| N | Beta [95% CI], \( p \) | Explained variance (%) |
|---|------------------------|------------------------|
| Base | 3636 | R\(^2\) = 25.3 |
| Lp(a)\(^a\) | 3639 | 0.11 [0.04; 0.18], 0.002 | 0.2 |
| Base | 3639 | R\(^2\) = 25.3 |
| Lp(a)\(^b\) ≥ 54.3 mg/dL vs. Lp(a) < 54.3 mg/dL | 3639 | 0.23 [0.005; 0.45], 0.05 | 0.1 |

\( N \): total number of participants. The models are adjusted for age and sex. \( ^a \)log-transformed Lp(a) levels, \( ^b \)Lp(a) ≥ 54.3 mg/dL vs. Lp(a) < 54.3 mg/dL. Explained variance is the difference in \( R^2 \) between each of the models and the base model.
Association of genetic variants with Lp(a)
The associations of SNPs with log-transformed Lp(a) are listed in Table 4. LPA rs10455872 and rs3798220 in the age- and sex-adjusted analyses were statistically significantly associated with log-transformed Lp(a) (beta per allele [95% CI], p: beta_rs10455872: 1.56 [1.46; 1.65], p < 0.0001 and beta_rs3798220: 1.51 [1.33; 1.69], p < 0.0001). The SNP rs10455872 in the age- and sex-adjusted analysis explained 24% of the variance in Lp(a). However, rs3798220 explained only 6.9% of the variance in Lp(a). The IL1F9 (rs13415097) SNP however, did not show any statistically significant association with Lp(a) (Table 4). The association between rs10455872 and rs3798220 with log-transformed Lp(a) remained statistically significant even after adjusting for risk factors (age, sex, smoking, BMI, HDL cholesterol, LDL cholesterol, triglyceride, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medication and lipid-lowering medication) (beta_rs10455872: 1.53 [1.43; 1.63], p < 0.0001 and beta_rs3798220: 1.46 [1.28; 1.64], p < 0.0001) (data not shown).

Mendelian randomization using genetically determined Lp(a) with coronary artery calcification
The Mendelian randomization analysis using the IVW method showed that Lp(a) is a causal risk factor for CAC, with an estimate of 0.27 per log-unit increase in Lp(a) levels (estimate [95% CI], p: 0.27 [0.11; 0.44], p = 0.001) (Table 5).

Discussion
In a large population-based Heinz Nixdorf Recall study, we investigated the association of Lp(a), LPA (rs10455872 and rs3798220) and IL1F9 (rs13415097) SNPs with coronary artery calcification. In our study, we found that i) LPA rs10455872 is associated with CAC, ii) the association between rs10455872 and CAC was attenuated after adjustment for Lp(a), iii) Lp(a) also showed an association with CAC, iv) both LPA SNPs were associated with Lp(a) and v) we did not find any evidence of an association of IL1F9 rs13415097 with Lp(a) or CAC. The association between rs10455872 and CAC remained statistically significant even after controlling for multiple testing. Using a Mendelian randomization approach, we found that genetically determined Lp(a) levels were causally associated with CAC.

Lp(a) is a cholesterol-rich particle having a covalently linked molecule of apolipoprotein B100 with a molecule of apo(a). We confirmed the previous association of both the LPA SNPs with the levels of Lp(a). Similar to a previous study, rs10455872 explained approximately 24% and rs3798220 explained 6.4% of the total variance of Lp(a) [4]. Observational studies have shown the association of Lp(a) with the risk of CAD [2, 3, 35, 36]. Moreover, genetic studies have shown the association of genetic variants in LPA with a higher risk for CAD, providing evidence for a causal role of Lp(a) in CAD [4–6]. Additionally, several observational studies looked at the role of Lp(a) on CAC, an important predictor for CAD. The result of the association between Lp(a) and CAC from the present study fits the findings of the studies showing a positive association between Lp(a) and CAC [10–12, 37, 38]. However, none of the observational studies systematically examined the association between Lp(a) and LPA genetic variants with CAC. Our study is the first to examine the association of Lp(a) as well as LPA genetic variants with CAC. Of the two LPA SNPs, only rs10455872 showed a statistically significant association with CAC. The association between rs10455872 and CAC was attenuated after adjusting for Lp(a), showing that Lp(a) levels mediate the effect of the rs10455872 SNP on CAC. The genetic association of the LPA variant with CAC provides evidence from a previous study showing that patients with CAD carrying LPA risk alleles have increased susceptibility to atherosclerotic manifestations and are more likely to be diagnosed earlier with CAD than are CAD cases not carrying these variants [39]. In addition, in vivo and in vitro studies have provided evidence that Lp(a) is present in coronary atherosclerotic plaques and plays a role in plaque inflammation and instability in atherosclerotic coronary arteries [40, 41]. The data of our study suggest that lifelong elevated levels of Lp(a) due to the LPA rs10455872 SNP might lead to an increase in coronary artery calcification that further leads to CVD events. However, it will be interesting to see if the results of our study could be replicated in other larger samples.

The present study is a population-based cohort study with data on Lp(a) levels, LPA and IL1F9 SNPs and measurement of CAC. Given the different distributions

| SNP         | N     | Beta [95% CI], p | Explained variance (%) |
|-------------|-------|------------------|------------------------|
| rs10455872  | 3311  | 1.56 [1.46; 1.65], < 0.0001 | 24                     |
| rs3798220   | 3780  | 1.51 [1.33; 1.69], < 0.0001 | 6.9                    |
| rs13415097  | 3773  | -0.01 [-0.08; 0.05], 0.63 | 0.15                   |

SNP Single nucleotide polymorphism, N: total number of participants in the analysis. The models are adjusted for age and sex.

| CAC | Causal estimate | 95% CI | p     |
|-----|----------------|--------|-------|
| IVW  | 0.27           | [0.11; 0.44] | 0.001 |

CAC Coronary artery calcification, IVW Inverse-variance weighted. Lp(a) was log-transformed.
of CAC in men and women gender-specific effects can be detected for CAC; however, due to moderate sample size gender stratified analyses could not be carried out in this study [11, 42].

Conclusions

In conclusion, we provide evidence for the association of LPA rs10455872, which is strongly associated with higher Lp(a) levels, and CAD is associated with higher levels of Lp(a) and CAC in our study. Our findings show that the rs10455872 SNP, through elevated Lp(a) levels, might play a role in promoting the development of atherosclerosis leading to CVD events.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12881-020-01003-3.

Additional file 1: Figure S1. Distribution of Lp(a) (mg/dL) according to the genotypes for LPA rs10455872 and rs3798220. Figure S2. Distribution of CAC (log(CAC + 1)) in strata of Lp(a) according to the genotypes for SNPs rs10455872, rs3798220 and rs13415007. Figure S3. Association between log-transformed Lp(a) with log(CAC + 1) in an unadjusted model. Figure S4. Association between Lp(a) and CAC score (Agastton) in quintiles of CAC in an unadjusted model.

Abbreviations

Lp(a): Lipoprotein(a); LPA: Lipoprotein (a) gene; IL1F9: Interleukin 1 family, member 9; CAC: Coronary artery calcification; SNP: Single nucleotide polymorphism; apoa: apolipoprotein; CAD: Coronary artery disease; GWAS: Genome-wide association studies; CVD: Cardiovascular disease; AVC: Aortic valve calcification; MVC: Mitral annular calcification; CT: Computer tomography; BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; IVW: Inverse-variance weighted; HWE: HARDY-Weinberg equilibrium; MAF: Minor allele frequency

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Authors’ contributions

Conceptualization: SP, AS, K-HJ, RE, SM; investigation: K-HJ, RE, AS, SM, AAM, MB-P; methodology: KHJ, RE, SM; acquisition of data: KHJ, RE, AS, SM, AAM, MB-P; analysis of data: SP; genotyping: PH, MMV; drafting of the manuscript: SP; all the authors reviewed, edited and approved the manuscript.

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Availability of data and materials

Due to data security reasons, i.e., the data contain potentially participant identifying information; the Heinz Nixdorf Recall study does not allow sharing data as a public use file. However, other authors/researchers are allowed to access data upon request, which is the same way the authors of the present paper obtained the data. Data requests can be addressed to recall@uk-essen.de.

Ethics approval and consent to participate

The study was approved by the ethical committee at the University Hospital of Essen, Germany and was conducted in accordance with the principles expressed in the Declaration of Helsinki. The study was certified and recertified according to DIN EN ISO 9001:2000/2008. All study participants gave their written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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