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Lipoprotein(a) is not associated with venous thromboembolism risk

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ABSTRACT

Objectives. Evidence from case-control studies as well as meta-analyses of these study designs suggest elevated lipoprotein(a) [Lp(a)] to be associated with an increased risk of venous thromboembolism (VTE). Prospective evidence on the association is limited, uncertain, and could be attributed to regression dilution bias. We aimed to assess the prospective association of Lp(a) with risk of VTE and correct for regression dilution. *Design.* We related plasma Lp(a) concentrations to the incidence of VTE in 2,180 men of the Kuopio Ischemic Heart Disease cohort study**.** Hazard ratios (HRs) (95% confidence intervals [CI]) were assessed and repeat measurements of Lp(a) at 4 and 11 years from baseline, were used to correct for within-person variability. *Results.* After a median follow-up of 24.9 years, 110 validated VTE cases were recorded. The regression dilution ratio of $\log_e$ Lp(a) adjusted for age was 0.85 (95% CI: 0.82-0.89). In analyses adjusted for several established risk factors and potential confounders, the HR (95% CI) for VTE per 1 SD (equivalent to 3.56-fold) higher baseline $\log_e$ Lp(a) was 1.06 (0.87-1.30). In pooled analysis of five population-based cohort studies (including the current study) comprising 66,583 participants and 1,314 VTE cases, the fully-adjusted corresponding HR for VTE was 1.00 (95% CI: 0.94-1.07), with no evidence of heterogeneity between studies. *Conclusions.* Primary analysis as well as pooled evidence from previous studies suggest circulating Lp(a) is not prospectively associated with future VTE risk, indicating that evidence of associations demonstrated in case-control designs may be driven by biases such as selection bias.

KEYWORDS

lipoprotein(a); venous thromboembolism; cohort study; risk factor; regression dilution

Introduction

Lipoprotein (a) [Lp(a)], composed of a dual structure and has both proatherosclerotic and prothrombotic functions [1,2], is an enigmatic lipoprotein that has been the subject of research over the past two decades. The relationship existing between Lp(a) and cardiovascular disease (CVD) has been well established. Consistently, several well-designed large-scale epidemiological studies have shown Lp(a) to be independently associated with cardiovascular outcomes [3-6] with some suggestions of causal relationships reported [4-6]. Though Lp(a) pathophysiology in vascular disease is controversial and still not fully understood, evidence suggests that Lp(a) contributes to the aetiology of vascular diseases via proatherosclerotic and proinflammatory mechanisms [7]. Venous thromboembolism (VTE) (comprising deep vein thrombosis (DVT) and pulmonary embolism (PE)), which is an important cause of increased morbidity and premature mortality [8,9], is closely linked with CVD [10-12] and both conditions share common antecedent risk factors [13]. Given the prothrombotic properties of Lp(a), it has been suggested that Lp(a) may play a role in the pathophysiology of VTE. Indeed, emerging data supports an association between elevated Lp(a) and VTE risk. Several case-control studies have shown increased VTE risk with elevated Lp(a) concentrations [14-17]. Two meta-analyses of these study designs have also confirmed these associations [18,19]. It appears the data showing a relationship between Lp(a) and VTE have largely been based on case-control designs, which are characterised by selection bias and do not show a temporal relationship between Lp(a) and VTE risk. A number of prospective cohort studies based in the general population have consistently reported no evidence of an association between Lp(a) and future VTE risk [20,21].

Based on the emerging data, it appears Lp(a) might not be prospectively linked to VTE risk, however more research is needed given that incident VTE rates in these previous studies were relatively small. Furthermore, there is a possibility that the inability of previous long-term follow-up cohort studies to demonstrate an association between Lp(a) and VTE risk could be partly attributed to regression dilution bias [22]. This is a phenomenon which potentially results in the underestimation of the true association between an exposure (Lp(a)

and outcome (VTE), particularly for cohorts with long-term follow-up. Regression dilution bias can be addressed by correcting the risk estimates using the regression dilution ratio (RDR) [23].

Due to the wide uncertainty in the evidence, we sought to evaluate in detail the prospective nature of the association between Lp(a) and future VTE risk using a population-based cohort of 2,180 men from eastern Finland followed up for over of 20 years. Secondly, repeat measurements of Lp(a) performed several years apart in a random sample of participants enabled quantification of within-person variability in Lp(a) levels. We also performed pooled analysis of available published prospective evidence on the association, thereby offering the opportunity to re-evaluate the nature and magnitude of the association in a larger representative sample of participants and VTE cases.

Methods

Study design and population

This study was conducted in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Appendix A**) [24]. The study population is based on the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a general population-based prospective cohort study designed to investigate risk factors for CVD and other chronic diseases. The design and recruitment methods of the KIHD study have been described in previous reports [25-30]. Participants consisted of a representative sample of men aged 42-61 years who were inhabitants of the city of Kuopio and its surrounding rural communities in eastern Finland. The actual baseline cohort consisted of 2,682 participants had baseline measurements performed between March 1984 and December 1989. In the current analysis, complete information on plasma Lp(a), relevant covariates, and VTE outcomes was available for 2,180 men. The research protocol was approved by the institutional review board of the University of Eastern Finland. All study procedures were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants

Assessment of Lp(a) and other risk markers

Assessment of data on demographics, lifestyle characteristics, physical measurements, collection of blood samples and measurement of serum lipids, lipoproteins and biochemical analytes have been described in previous reports [27,29]. Blood samples were taken between 8 and 10 a.m. after an overnight fast. The cholesterol content of lipoprotein fractions were measured from fresh samples after combined ultracentrifugation and precipitation, and were assessed enzymatically (Boehringer Mannheim, Mannheim, Germany) [31]. Lp(a) measurements were made from frozen plasma samples stored at -20° C for 2-6 years, using a radioimmunoassay (Mercodia Apo(a) RIA, Mercodia AB, Uppsala, Sweden), with repeat measurements performed in a random subset of participants at 4 years and 11 years after the baseline measurements. Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Serum high sensitivity C-reactive protein (hsCRP) measurements were made with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). For the assessments of age, lifestyle factors such as smoking and alcohol consumption, medical conditions, and medication history; participants completed self-administered questionnaires [32]. The energy expenditure of physical activity was assessed using the validated KIHD 12-month leisure-time physical activity questionnaire [33,34]. Body mass index (BMI) was estimated as weight in kilograms divided by the square of height in meters.

Ascertainment of incident VTE

We included all first lifetime VTE events that occurred from study enrollment through to 2013. These were identified by computer linkage to the National Hospital Discharge Registry data and a comprehensive review of available hospital records, wards of health centres, health practitioner questionnaires, death certificate and autopsy registers, and medico-legal reports. The diagnosis of DVT or PE required positive imaging tests. Documents were cross-checked

in detail and VTE events were validated by two physicians. No losses to follow-up were recorded as all participants in the KIHD study (using Finnish personal identification codes) are under continuous surveillance for the development of new outcomes including VTE cases.

Statistical analysis

Prospective cohort analyses Skewed variables (hsCRP, triglycerides, and fibrinogen) were log transformed to achieve approximately symmetrical distributions. Descriptive analyses were conducted to summarize the baseline characteristics of the participants, with means (standard deviation, SD) or medians (interquartile range, IQR) reported for continuous variables and n (percentages) for categorical variables. The partial correlation coefficients were calculated using linear regression models adjusted for age, to assess the cross-sectional associations of Lp(a) with various risk markers. The SD of baseline loge Lp(a) concentration was 1.27, corresponding to approximately four-fold higher circulating Lp(a) (ie, $e^{1.27}$=3.56). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models, after confirming no major departure from the assumptions of proportionality of hazards using Schoenfeld residuals.[35] Lp(a) was modelled continuously (per1 SD (ie, 3.56 fold) higher Lp(a) levels) and by quartiles defined according to the baseline distribution of plasma Lp(a) levels. Hazard ratios were calculated with adjustment for confounders in two models: i) age and ii) established risk factors and other potential confounders [BMI, systolic blood pressure (SBP), history of hypertension, prevalent coronary heart disease (CHD), smoking status, history of diabetes, total cholesterol, lipid lowering medication, estimated glomerular filtration rate (eGFR) as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [36], physical activity, alcohol consumption, prevalent cancer, fibrinogen and hsCRP. We employed formal tests of interaction to assess statistical evidence of effect modification on the association by categories of pre-specified clinically relevant individual level characteristics. To quantify and correct for within-person variability in Lp(a) levels, which is, the extent to which an individual's Lp(a) measurements vary around the long-term average exposure levels ("usual

levels") [37], adjusted regression dilution ratios (RDRs) were calculated by regressing available repeat measurements of Lp(a) on baseline values [23]. The RDR assumes that the "usual levels" of Lp(a) represents the true long-term exposure of Lp(a) levels on VTE risk.

Systematic review and meta-analysis We conducted a meta-analysis of published prospective cohort studies reporting on the association between Lp(a) and risk of VTE, using a predefined protocol and reported in accordance with PRISMA and MOOSE guidelines [38,39] (**Appendix B and C**). Published observational population-based prospective (cohort, case cohort, or nested case-control) studies that evaluated the associations between baseline levels of Lp(a) and risk of first VTE in the adult general population up to July 2018, were sought using computer-based databases (MEDLINE, EMBASE, and Web of Science). Case-control study designs were not part of the inclusion criteria. The computer-based searches combined free and MeSH search terms and combined key words related to the exposure (e.g., "lipoprotein(a)") and outcome (e.g., "venous thromboembolism", "deep vein thrombosis", "pulmonary embolism"). We placed no restrictions on language or the publication date. Details of the search strategy are reported in **Appendix D**. We assessed study quality using the nine-star Newcastle–Ottawa Scale (NOS)[40] as described previously [41]. Summary measures were presented as relative risks (RRs) with 95% confidence intervals (CIs). Following Cornfield's rare disease assumption [42], hazard ratios and odds ratios were assumed to approximate the same measure of RR. To enable a consistent approach to the meta-analysis and enhance comparison with the primary analysis, reported study-specific risk estimates were also transformed to per SD increase in Lp(a) or as extreme quartiles of Lp(a) using standard statistical methods [43,44], which have been described in detail previously [45,46]. Summary RRs were pooled using a random effects model to minimize the effect of between-study heterogeneity [47]. Subsidiary analysis used fixed effects models. Statistical heterogeneity between studies was quantified using standard chi-square tests and the I^2 statistic [48]. All statistical analyses were conducted using Stata version 15 (Stata Corp, College Station, Texas).

Results

Baseline characteristics of Lp(a) and correction for within-person variability

The mean baseline age of study participants was 53 (SD, 5) years and the median (IQR) of Lp(a) at baseline was 9.66 (3.75-22.27) mg/dl (**Table 1**). Plasma Lp(a) levels were weakly correlated with several risk markers. There were inverse correlations of Lp(a) with BMI, triglycerides, and FPG; whereas, positive correlations were observed for total cholesterol, creatinine, fibrinogen, and hsCRP. Repeat measurements of Lp(a) taken 4 years and 11 years after baseline were available in a random sample of 691 men, providing a total of 1,360 repeat measurements of Lp(a). Overall, the regression RDR of loge Lp(a), adjusted for age, was 0.85 (95% CI: 0.82 to 0.89), suggesting that the associations using baseline measurements of Lp(a) with VTE would under-estimate the association by [(1/0.85)-1]*100=18%.

Lipoprotein(a) and risk of VTE

Prospective cohort results During a median follow-up of 24.9 (interquartile range, 17.9-27.1) years, 110 VTE cases (annual rate 2.32/1,000 person-years at risk; 95% CI: 1.93 to 2.80) were recorded. The HR per 1 SD change in baseline $\log_e$ Lp(a) concentration was 1.06 (95% CI: 0.88 to 1.29; p=0.530) in age-adjusted analysis, which remained consistent on further adjustment for several established risk factors and potential confounders 1.06 (95% CI: 0.87 to 1.30; p=0.537) (**Table 2)**. The null associations were maintained in analyses by quartiles of the baseline distribution of Lp(a) levels (**Table 2**). The findings were also similar on correction for regression dilution (**Table 2**). In further analysis that compared Lp(a) concentrations > 30 mg/dl with that ≤ 30 mg/dl, no evidence of any association was observed. Hazard ratios did not vary importantly by several relevant clinical characteristics (**Figure 1**).

Meta-analysis of published studies We identified four population-based prospective cohort studies reporting on the associations between circulating Lp(a) and VTE risk (**Appendices E and F**).[20,21,49,50] Including the current study, the pooled analysis involved five studies

comprising 66,583 participants and 1,314 VTE cases. The pooled RR for VTE per 1 SD higher baseline $\log_e$ Lp(a) in fully-adjusted analyses was 1.00 (95% CI: 0.94 to 1.07) (I^2=0%, 95% CI: 0 to 79%; *P*=0.576) (**Figure 2**). The corresponding RR was 1.00 (95% CI: 0.84 to 1.19) when comparing the top versus bottom quartiles of Lp(a) levels. When a fixed effect model was employed, the summary RRs were identical to that of random-effects meta-analysis.

Discussion

Summary of main findings

In this population-based prospective study of middle-aged men without a history of VTE at study entry, our analysis showed no evidence of an association of circulating Lp(a) with risk of VTE. The association did also not vary importantly across several clinically relevant subgroups. Our reproducibility studies of Lp(a) yielded a high RDR which indicates that Lp(a) concentration is consistent within individuals over several years. Pooled estimates of five prospective studies (including the current study) confirmed our finding of no evidence of an association in the primary cohort analysis and there was no evidence of heterogeneity between the contributing studies.

Comparison with previous work

Several reports based on case-control designs have reported on the associations between circulating Lp(a) and VTE risk. Though the findings from these reports have been mixed, majority have generally shown an increased risk of VTE with elevated Lp(a) [14-17]. There have also been efforts to aggregate these data resulting in two published reviews on the topic. In the earlier review, Sofi and colleagues pooled the results of six case-control studies and showed a significant association between high Lp(a) levels and VTE risk [18]. In a more recent review, Dentali and colleagues pooled the results of 14 studies and also demonstrated Lp(a) to be associated with an increased risk of VTE [19]. Of all 14 studies included in this review, only one prospective cohort was included and this was the study conducted by

Kamstrup et al [20]. Indeed, data showing evidence of an association between circulating Lp(a) and VTE risk seems to be based on case-control study designs. Unfortunately, these study designs are characterised by selection bias and are not able to adequately address temporality. Prior to the current study, four large-scale prospective cohort studies based in the general population and with long-term follow-up for VTE events have all consistently shown that circulating Lp(a) is not associated with VTE risk [20,21,49,50]. Though these previous studies did not correct for regression dilution bias, our current analysis shows that risk estimates based on baseline and repeated measures corresponded well. Results from the KIHD prospective study as well as pooled analysis of available prospective evidence indicate that Lp(a) is not associated with risk of VTE.

Possible explanations for findings

As with all observational cohort studies, exposure or risk factor levels are usually assessed at study entry and related to outcomes which occur after several years. However, due to random measurement errors, temporary fluctuations and changes in the exposure over time, the effect and value of the exposure changes with time leading to regression dilution bias [22]. This potentially results in the underestimation of the true association between an exposure and outcome, particularly for cohorts with long-term follow-up. It can be argued that the absence of an association between Lp(a) and VTE in previous cohorts could be potentially explained by the phenomenon of regression dilution. However, this is unlikely given that we found no evidence of an association despite correcting for regression dilution. Furthermore, reproducibility substudies of Lp(a) in the KIHD and that of other large-scale cohort studies[3] indicate that analyses using only single baseline measurements of Lp(a) does not underestimate the associations between Lp(a) and outcomes. There is established evidence that Lp(a) is associated with CVD outcomes and it has been suggested that the pathophysiological mechanisms underlying the associations may relate to the pro-atherogenic, prothrombotic, and pro-inflammatory properties of Lp(a) [7]. Given the prothrombotic and antifibrinolytic properties of Lp(a) [2], the closely linked nature of CVD and VTE [10-12],

and the emerging evidence from both epidemiological and clinical studies; there is a growing debate that Lp(a) may also be linked to the development of VTE. The current data which is based on prospective evidence does not support this suggestion and it is possible that Lp(a) may not be an emerging risk factor for VTE. Spence and Koschinsky also argue that the effects of Lp(a) on VTE risk may only be evident at the highest concentrations of Lp(a) [51], which we were not able to prove in the current study. However, mechanistic conclusions underlying the association between Lp(a) and VTE cannot be drawn from observational epidemiological studies and further studies on mechanisms are warranted.

Strengths and limitations

Compared to previous prospective cohort studies, the current study had the advantage of being a well-characterised cohort of men who were nationally representative; involved a high response rate, a long-follow-up period of over 20 years with no loss to follow-up; and comprehensive analysis with adjustment for a broad panel of lifestyle and biological markers as well as stratified analyses by several clinical relevant characteristics. An important strength of the current study is that repeat measurements of Lp(a) made within a random subset of individuals over time after baseline were available, which enabled correction for the extent of within-person variability in Lp(a) over the long period of follow-up. Finally, we were able to conduct a pooled analysis of previous studies including the current study, to put the findings into wider context. In our pooled analysis, there was no evidence of heterogeneity between contributing studies. Our study was characterized by the following limitations: (i) we included only middle-aged men based on a predominantly white-European population from eastern Finland and given that plasma levels of Lp(a) may vary substantially between different populations [52], our findings therefore cannot be generalized to women, the young, and other ethnicities; (ii) we had data on only all VTEs which precluded the ability to conduct subgroup analyses of type of specific VTE outcomes such as idiopathic VTE or that due to cancer; and (iii) inability to adjust for other potential confounders such incident cancer, family history of VTE, and use of antithrombotic drugs.

Conclusions

Primary cohort analysis as well as pooled evidence from previous studies suggest that circulating Lp(a) is not prospectively associated with future VTE risk. This comprehensive report indicates that the associations demonstrated in previous studies may be driven by features and limitations of study designs employed.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Table 1. Baseline participant characteristics of the KIHD cohort overall and by quartiles of lipoprotein(a)

	Overall (N=2,180) Mean (SD) or median (IQR) or n (%)	**Quartile 1 Mean (SD) or median (IQR) or n (%)**	**Quartile 2 Mean (SD) or median (IQR) or n (%)**	**Quartile 3 Mean (SD) or median (IQR) or n (%)**	**Quartile 4 Mean (SD) or median (IQR) or n (%)**	**Pearson correlation r (95% CI)†**
Lipoprotein(a) (mg/dl)	9.66 (3.75-22.27)	1.61 (0.90-2.73)	6.23 (4.88-7.84)	15.0 (12.3-18.5)	36.8 (28.5-51.8)	-
Questionnaire/Prevalent conditions						
Age at survey (years)	53 (5)	53 (5)	53 (5)	53 (5)	53 (5)	0.01 (-0.03, 0.05)
Alcohol consumption (g/week)	31.9 (6.4-92.8)	30.1 (6.4-96.0)	28.4 (6.1-88.4)	32.9 (6.1-96.9)	35.5 (7.6-88.5)	-0.00 (-0.05, 0.04)
History of diabetes	87 (4.0)	31 (5.7)	26 (4.8)	20 (3.7)	10 (1.8)	-
Current smokers	669 (30.7)	161 (29.5)	165 (30.2)	168 (30.9)	175 (32.1)	-
History of hypertension	653 (30.0)	178 (32.7)	162 (29.7)	148 (27.2)	165 (30.3)	-
History of CHD	546 (25.1)	157 (28.8)	131 (24.0)	122 (22.4)	136 (25.0)	-
History of cancer	36 (1.7)	11 (2.0)	11 (2.0)	7 (1.3)	7 (1.3)	-
Lipid lowering medication	14 (0.6)	5 (0.9)	2 (0.4)	1 (0.2)	6 (1.1)	-
Physical measurements						
BMI (kg/m^2)	26.9 (3.5)	27.6 (3.9)	26.7 (3.4)	26.8 (3.3)	26.6 (3.4)	-0.10 (-0.14, -0.06)***
SBP (mmHg)	134 (17)	135 (17)	133 (16)	134 (17)	133 (17)	-0.04 (-0.08, -0.00)
DBP (mmHg)	89 (10)	89 (11)	88 (10)	89 (11)	88 (10)	-0.04 (-0.08, 0.00)
Physical activity (kj/day)	1192 (621-1987)	1231 (662-1991)	1160 (669-1998)	1104 (58.-1891)	1275 (612-2021)	-0.03 (-0.07, 0.02)
Lipid markers						
Total cholesterol (mmol/l)	5.91 (1.08)	5.73 (1.02)	5.88 (1.09)	5.88 (1.12)	6.12 (1.05)	0.12 (0.08, 0.16)***
HDL-C (mmol/l)	1.30 (0.30)	1.31 (0.32)	1.30 (0.28)	1.30 (0.30)	1.29 (0.30)	-0.01 (-0.05, 0.03)
Triglycerides (mmol/l)	1.10 (0.81-1.56)	1.15 (0.84-1.68)	1.08 (0.78-1.58)	1.10 (0.82-1.52)	1.10 (0.79-1.55)	-0.06 (-0.10, -0.02)*
Metabolic, renal, and inflammatory markers						
Fasting plasma glucose (mmol/l)	5.35 (1.26)	5.50 (1.52)	5.34 (1.20)	5.34 (1.19)	5.23 (1.07)	-0.07 (-0.11, -0.03)**
Serum creatinine (µmol/1)	89.4 (13.7)	88.6 (12.1)	89.1 (13.5)	89.0 (14.9)	91.0 (14.0)	0.04 (0.00, 0.08)*
Estimated GFR ($ml/min/1.73\ m^2$)	86.9 (17.1)	87.4 (15.0)	87.7 (20.5)	87.5 (16.2)	85.2 (16.2)	-0.03 (-0.08, 0.01)
Fibrinogen (g/l)	2.96 (2.63-3.33)	2.91 (2.58-3.28)	2.95 (2.63-3.31)	2.97 (2.68-3.32)	3.00 (2.67-3.44)	0.08 (0.03, 0.12)**
High sensitivity CRP (mg/l)	1.27 (0.70-2.38)	1.17 (0.61-2.25)	1.20 (0.65-2.34)	1.34 (0.76-2.37)	1.35 (0.80-2.73)	0.09 (0.05, 0.13)***

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; Lp(a), lipoprotein(a)

HDL-C, high-density lipoprotein cholesterol; KIHD, Kuopio Ischemic Heart Disease; SD, standard deviation; SBP, systolic blood pressure;

VTE, venous thromboembolism; asterisks indicate the level of statistical

significance: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$, †Pearson correlation coefficients

between $\log_e$ Lp(a) and the row variables

Table 2. Association of Lp(a) and venous thromboembolism in the KIHD cohort

Plasma Lp(a) (mg/dl)	Events/ Total	Person-time at risk	Model 1	Model 2
			HR (95% CI)	HR (95% CI)
		Baseline Lp(a)		
Per 1 SD increase in log Lp(a)	110 / 2,180	47,400	1.06 (0.88 to 1.29)	1.06 (0.87 to 1.30)
Q1 (0.56-3.74)	25 / 545	11,810	ref	ref
Q2 (3.75-9.66)	30 / 546	11,980	1.19 (0.70 to 2.03)	1.24 (0.72 to 2.12)
Q3 (9.67-22.26)	25 / 544	11,914	0.99 (0.57 to 1.72)	1.02 (0.58 to 1.79)
Q4 (> 22.26)	30 / 545	11,695	1.23 (0.72 to 2.09)	1.25 (0.72 to 2.15)
		Usual Lp(a)*		
Per 1 SD increase in log Lp(a)	110 / 2,180	47,400	1.07 (0.86 to 1.35)	1.08 (0.85 to 1.36)
Q1 (0.56-3.74)	25 / 545	11,810	ref	ref
Q2 (3.75-9.66)	30 / 546	11,980	1.23 (0.66 to 2.30)	1.29 (0.68 to 2.42)
Q3 (9.67-22.26)	25 / 544	11,914	0.98 (0.51 to 1.89)	1.02 (0.52 to 1.98)
Q4 (> 22.26)	30 / 545	11,695	1.28 (0.68 to 2.38)	1.29 (0.68 to 2.47)

CI, confidence interval; HR, hazard ratio; KIHD, Kuopio Ischemic Heart Disease; Lp(a), lipoprotein(a); Q, quartile; ref, reference; SD, standard deviation;

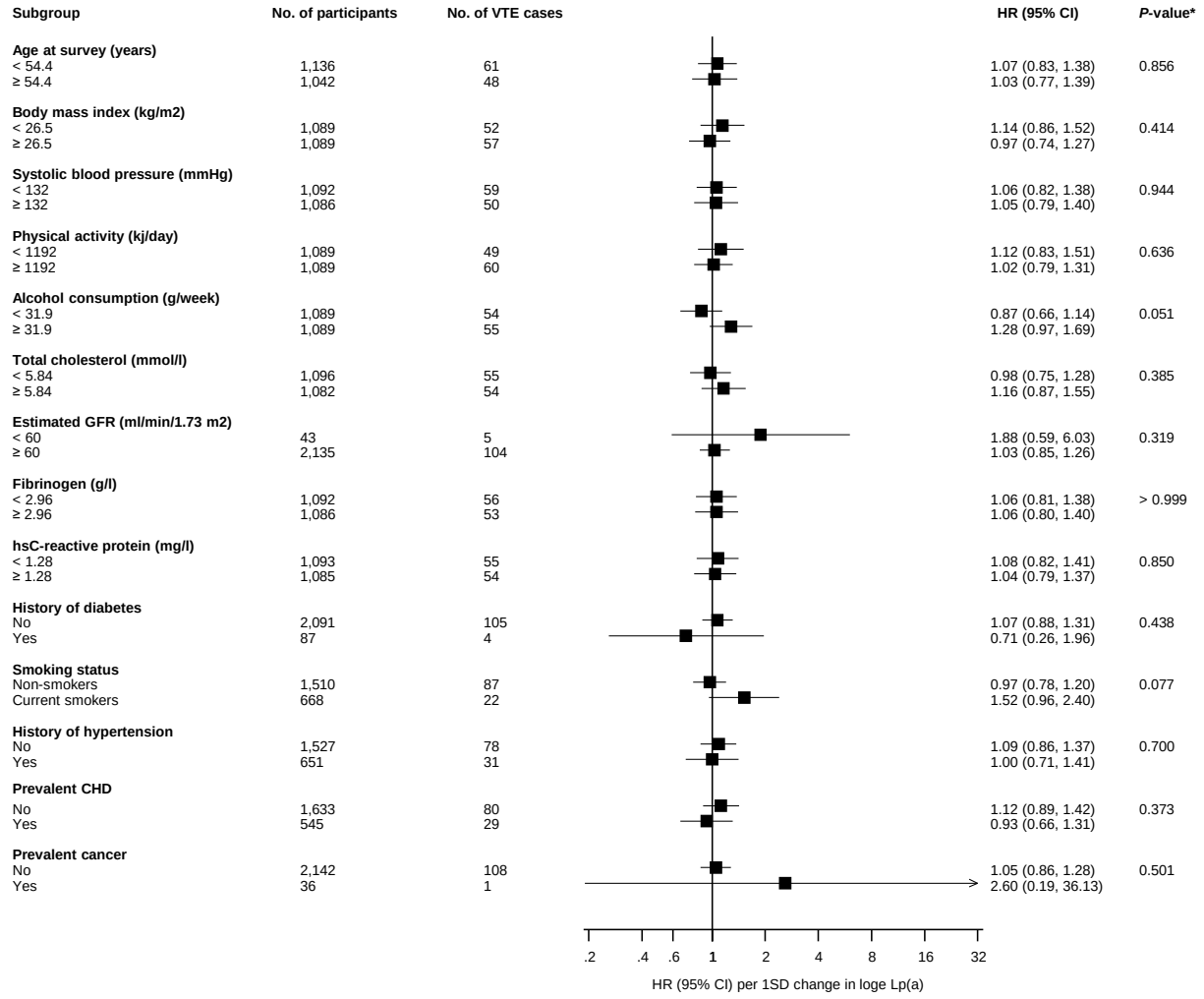
*, indicates correction for within-person variability in values of Lp(a), that is, the extent to which an individual's Lp(a) measurements vary around a long-term average value ("usual Lp(a) values"); the SD of loge Lp(a) concentration is 1.27, corresponding to approximately four-fold higher circulating Lp(a) (ie, $e^{1.27}=3.56$)

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, triglycerides, lipid medication, estimated glomerular filtration rate, physical activity, alcohol consumption, prevalent cancer, fibrinogen, and high sensitivity C-reactive protein

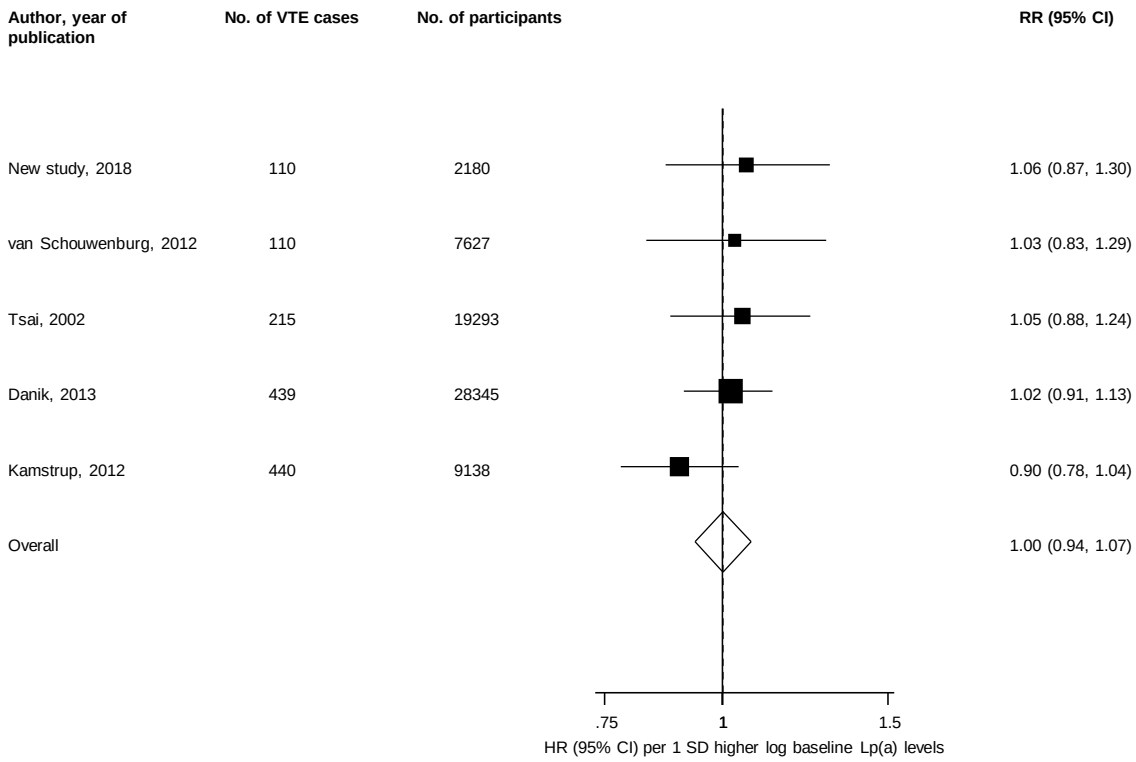
Figure legends

Figure 1. Hazard ratios for baseline levels of lipoprotein(a) and venous thromboembolism risk by several participant level characteristics in the KIHD cohort



Hazard ratios are reported per 1 standard deviation increase in $\log_e$ lipoprotein(a); hazard ratios were adjusted for age, body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, triglycerides, lipid medication, estimated glomerular filtration rate, physical activity, alcohol consumption, prevalent cancer, fibrinogen, and high sensitivity C-reactive protein; CHD, coronary heart disease; CI, confidence interval; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; KIHD, Kuopio Ischemic Heart Disease; Lp(a), lipoprotein(a); SD, standard deviation; *, *P*-value for interaction

Figure 2. Prospective studies of lipoprotein(a) and risk of venous thromboembolism included in meta-analysis



The summary estimates presented were calculated using random effects models; relative risks are reported per 1 standard deviation (SD) increase in lipoprotein(a); sizes of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); RR, relative risk; VTE, venous thromboembolism

SUPPLEMENTARY MATERIAL

Appendix A	STROBE Statement
Appendix B	PRISMA checklist
Appendix C	MOOSE checklist
Appendix D	Literature search strategy
Appendix E	Flow of studies included in pooled analysis
Appendix F	Characteristics of prospective studies included in meta-analysis

Appendix A. STROBE Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 3-4
Methods			
Study design	4	Present key elements of study design early in the paper	Study design and population
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study design and population
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Study design and population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Assessment of Lp(a) and other risk markers
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Assessment of Lp(a) and other risk markers
Bias	9	Describe any efforts to address potential sources of bias	Statistical analysis
Study size	10	Explain how the study size was arrived at	Statistical analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical analysis
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Statistical analysis
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Study design and population

		(b) Give reasons for non-participation at each stage	Study design and population
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Results; Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results; Figure 1
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion - Summary of main findings
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12

Appendix B. PRISMA check-list

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix D
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Appendix E
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Appendix F
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Appendix F
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results and Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion

Section/topic	Item No	Checklist item	Reported on page No
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	None

Appendix C. MOOSE checklist

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Elevated circulating lipoprotein(a) has been suggested to the linked to the development of venous thromboembolism (VTE), but the prospective nature of the association is uncertain.
√	Hypothesis statement	There is no prospective association between Lp(a) and VTE risk.
√	Description of study outcomes	VTE
√	Type of exposure	Blood levels of Lp(a)
√	Type of study designs used	Prospective (cohort, case-cohort or "nested case control") population-based studies
√	Study population	Approximately general populations with no prevalent VTE at baseline
Reporting of search strategy should include		
√	Qualifications of searchers	Setor Kunutsor, MD PhD; Jari Laukkanen, MD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception of MEDLINE, EMBASE, Web of Science to 18 July 2018. **Search strategy:** In Appendix 4.
√	Databases and registries searched	MEDLINE, EMBASE, and Web of Science
√	Search software used, name and version, including special features	Ovid was used to search EMBASE Endnote used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language
√	Method of handling abstracts and unpublished studies	None found
√	Description of any contact with authors	Not applicable
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Heterogeneity of the studies was explored with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses are detailed in the methods. We performed random effects meta-analysis with Stata 15.

√	Provision of appropriate tables and graphics	Figure 2 and Appendix F
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Appendix F
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	There was no evidence of heterogeneity between contributing studies.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussed in the context of the results.
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	Assessment of the mechanistic pathways underlying the link between Lp(a) and VTE
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

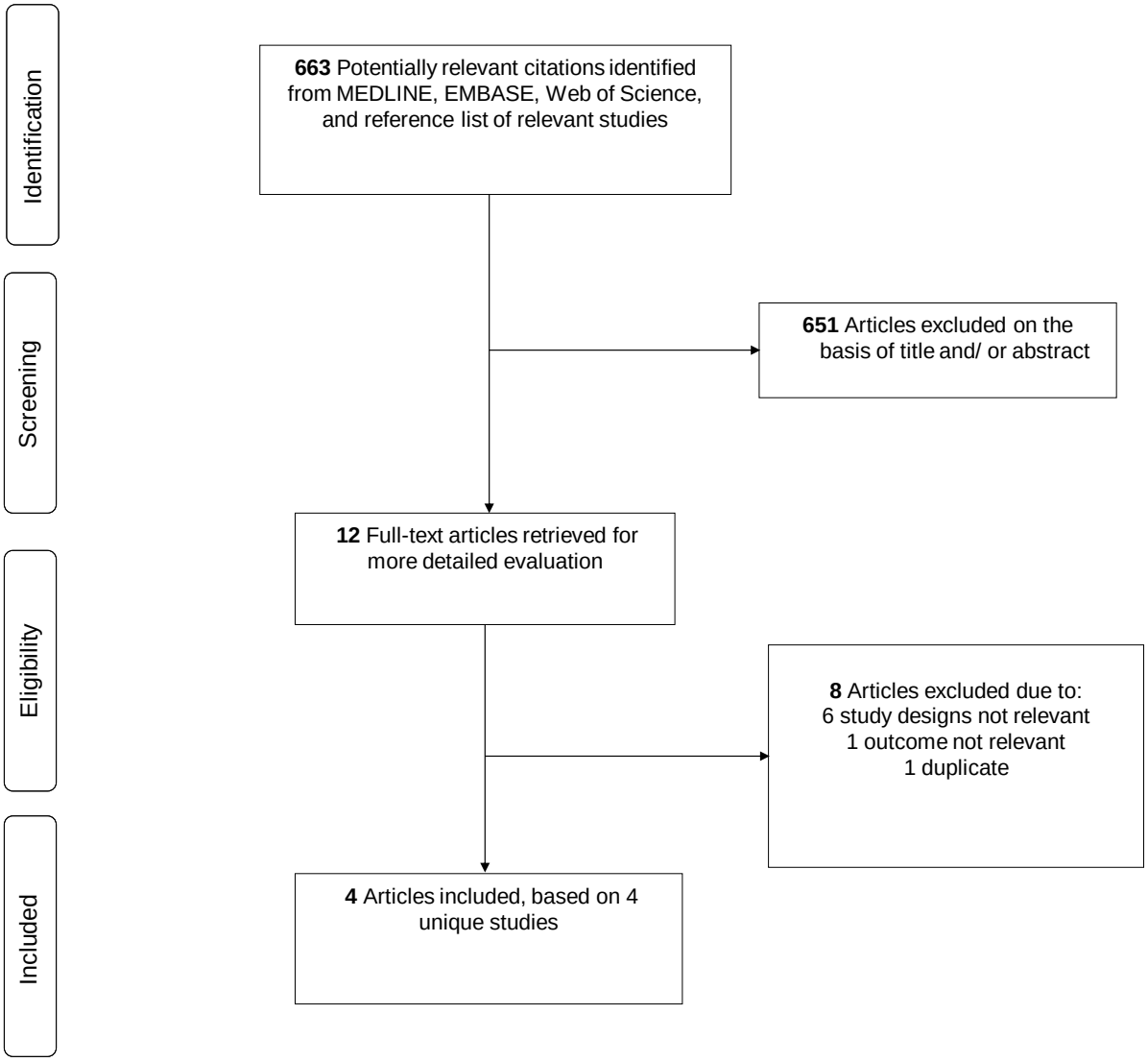
Appendix D. Literature search strategy

Relevant studies published before 18 July, 2018 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, and the Science Citation Index databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles) and by hand searching of relevant journals. The computer-based searches combined search terms related to lipoprotein(a) and venous thromboembolism without language restriction.

1 exp "Lipoprotein(a)"/ (4776)
2 exp Venous Thromboembolism/ (8367)
3 exp Venous Thrombosis/ (51541)
4 exp Pulmonary Embolism/ (36297)
5 2 or 3 or 4 (86213)
6 1 and 5 (79)
7 limit 6 to humans (79)

Parts i, ii and iii were combined using 'AND' to search MEDLINE. Each part was specifically translated for searching alternative databases.

Appendix E. Flow of studies included in pooled analysis



Appendix F. Characteristics of prospective studies included in meta-analysis

Lead author, publication year [Reference]	Name of study	Location of study	Year(s) of baseline survey	Baseline age (years)	% male	Mean/median duration of follow-up (years)	Total no. of participants	No. of VTE cases	Covariates adjusted for	Study quality
Tsai, 2002 [21]	LITE	USA	1987-1998	59.0	45.0	8.0	19,293	215	Age, race, and sex	8
Kamstrup, 2012 [20]	CCHS	Denmark	1991-1994	58.0	44.0	13.0	9,138	440	Age, sex, BMI, smoking, physical activity, menopausal status, HRT, oral contraceptives	9
van Schouwenburg, 2012 [50]	PREVEND	Netherlands	1997-1998	49.0	49.0	10.5	7,627	110	Age, sex, hypertension, DM, CRP, BMI, eGFR, smoking	7
Danik, 2013 [49]	WHS	USA	1992-1995	54.2	0.0	14.4	28,345	439	Age, smoking, BMI, hormone therapy status, exercise level and randomization treatment arms	7
Current study, 2018	KIHD	Finland	1984-1989	42-61	100.0	24.9	2,180	110	Age, BMI, SBP, history of hypertension, prevalent CHD, smoking, history of DM, total cholesterol, Triglycerides, lipid medication, eGFR, physical activity, alcohol consumption, prevalent cancer, fibrinogen, hsCRP	8
Total							66,583	1,314		

BMI, body mass index; CHD, coronary heart disease; CCHS, Copenhagen City Heart Study; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HRT, hormone replacement therapy; hsCRP, high sensitivity C-reactive protein; KIHD, Kuopio Ischemic Heart Disease; LITE, The Longitudinal Investigation of Thromboembolism Etiology; NR, not reported; PREVEND, Prevention of Renal and Vascular End-stage Disease; SBP, systolic blood pressure; WHS, Women's Health Study