THE LANCET

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The Lp-PLA$_2$ Studies Collaboration. Lipoprotein-associated phospholipase A$_2$ and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 2010; **375:** 1536–44.

Web Extra material

eAppendices

eFigures

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eAppendix 1. Acronyms of studies included in the Lp-PLA$_2$ Studies Collaboration

ARIC,[1,2] Atherosclerosis Risk In Communities study
Bruneck,[3] The Bruneck study
CHS,[4] Cardiovascular Health Study*
EPIC-Norfolk,[5] European Prospective Investigation into Cancer – Norfolk
FHS Offspring,[6] Framingham Heart Study Offspring Study
FRISC-II,[7] Fragmin and fast Revascularisation in InStabilitiy in Coronary artery disease trial II
GENICA,[8] Genetic and Environmental factors in Coronary Atherosclerosis
GUSTO-IV,[7] Global Utilitzation of Strategies to Open Occluded Arteries IV
HPFS,[9] Health Professionals Follow-up Study
HPS,[10] Heart Protection Study
IHCS,[11] Intermountain Heart Collaborative Study
KAROLA,[12] Langzeiterfolge der KARdiOLogischen Anschlussheilbehandlung
LURIC,[13] Ludwigshafen Risk and Cardiovascular Health Study
MCOC,[14] Mayo Clinic – Olmsted County
MCRP,[15] Mayo Clinic – Referral practice
MDCS,[16,17] Malmö Diet and Cancer Study
MONICA-KORA,[18] Monitoring Trends and Determinants in Cardiovascular Disease – KORA survey
NHS,[9] Nurses Health Study
NOMAS,[19] Northern Manhattan Study
NPHS-II,[20] Northwick Park Heart Study II
OPUS-TIMI 16,[21] Orbofiban in Patients with Unstable Coronary Syndromes – Thrombolysis In Mycocardial Infarction 16
PEACE,[22] Prevention of Events with Angiotensin Converting Enzyme Inhibition
PROSPER,[23] Prospective Study of Pravastatin in the Elderly at Risk
PROVEIT-TIMI 22,[21] PRavastatin Or atorVastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22
Rancho Bernardo,[24] The Rancho Bernardo Study
Rotterdam,[25] The Rotterdam study
SDVC,[26] San Diego Vascular Cohort study
THROMBO,[27] Thrombogenic Factors and Recurrent Coronary Events
WHI-HaBPS,[28] Women's Health Initiative - Hormones and Biomarkers Predicting Stroke in Women
WHS,[29] Women's Health Study
WOSCOPS,[30] West of Scotland Coronary Prevention Study.

* In the current analysis, the CHS was analysed as two separate studies (CHS-1 and CHS-2) stratified by ethnicity, yielding 32 studies overall

eAppendix 2. Data collection and statistical methods

Study selection criteria Eligible prospective studies (reported variously as observational cohort studies, clinical trials, nested case-control or case-cohort subsets) had data on Lp-PLA_2 mass and/or activity available from baseline measurements and information on cause-specific mortality and/or major cardiovascular morbidity collected during follow-up.[1-30] Studies were identified through computer-assisted literature searches of databases, scanning of reference lists, hand-searching of relevant journals, correspondence with authors of relevant reports and consultation with experts in the field. As only two studies invited to participate could not provide data,[31,32] >95% of relevant incident cardiovascular cases in known studies are estimated to have been included.

Data collection A more detailed description of data collection has been published previously.[33] Briefly, anonymised data were sought from collaborators on many characteristics recorded at the baseline survey and at subsequent surveys during follow-up. Information on categorical variables, such as alcohol consumption status, physical activity and smoking status, was systematically re-coded to maximise comparability among studies. For each individual, data were sought on the following outcomes and on their dates of occurrence: non-fatal CHD; non-fatal stroke; cause-specific mortality (or at least fatal CHD and fatal stroke) and other cardiovascular outcomes. Precise details of the diagnostic criteria used for the definition of incident cases were sought from each study (as were data on the completeness of follow-up). Principal analyses were based on events classified according to the International Classification of Diseases (ICD) or, where this was not available, on study-specific classification systems. Attribution of death referred to the primary cause provided (or, in its absence, the underlying cause provided). Data obtained from each participating study were checked for internal consistency and any queries then referred back, in confidence, to the study collaborator(s), before harmonisation to a standard format. The content of the data was unchanged by this process, and computer-generated detailed summary tabulations based on the converted data were reviewed and confirmed by collaborators. Data are stored securely and anonymously at the coordinating centre.

Statistical methods Because of substantial differences in the mean and standard deviation (SD) of Lp-PLA_2 levels observed across contributing studies, levels were Z-transformed to a mean of 0 and a SD of 1 within each study. 95% confidence intervals (CIs) and two-sided p-values were used. Studies contributing 10 or fewer outcomes to any particular analysis were excluded.

Regression analyses − The main analyses were based on Cox proportional hazards (PH) models[34] estimated for each study separately, with logistic regression used for "nested" case-control studies (see below). The PH models have been stratified by sex, baseline history of disease and, if applicable, randomised group. So for each study s=1…S, with strata k=1…K_s (for most studies K_s=2 just for the two sexes) and individuals i=1…n_s with exposure of interest E_{si} and other covariates $\boldsymbol{X}_{si}$, the hazard at time t after baseline has been modelled as:

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si} \qquad (1)$$

The evolution of risk over time has thus been modelled independently for each stratum in each study, as represented by the non-parametric baseline hazards $h_{0sk}(t)$. The β_s are the parameters of interest, being the log hazard ratios per unit increase in the exposure in study s, adjusted for the confounding effects of the covariates $\boldsymbol{X}_{si}$. These estimated log hazard ratios have been combined over studies using random-effects meta-analysis. Parallel analyses involved fixed effect models. Writing the variance of the estimated β_s as v_s, the random-effects meta-analysis model is:

$$\hat{\beta}_s = \beta_s + \varepsilon_s; \text{where } \varepsilon_s \sim N(0, v_s)$$
$$\beta_s = \beta + \eta_s; \text{where } \eta_s \sim N(0, \tau^2) \qquad (2)$$

Here β is the average log hazard ratio, whose estimate combines within-study information on the relationship between exposure and risk, while allowing for heterogeneity between studies as represented by the variance τ^2, although potential sources of heterogeneity were specifically investigated (see below). A standard moment estimator of τ^2 was used.[35] Nested case-control studies were analysed with similar methods to those described above, but involved logistic regression.[36] For individually-matched studies, conditional logistic regression was used, whereas unconditional logistic regression was used in frequency-matched studies, including matching factors as covariates. Such analyses either provided estimates of hazard ratios (if matched controls were selected

to be disease-free at the time the case had an event), or odds ratios (if the selected controls were disease-free at the end of the study). Hazard ratios and odds ratios were assumed to approximate the same underlying relative risk. For nested case-cohort studies, weighted analyses allowed for the fact that by design cases who were not in the randomly selected sub-cohort were also included in the analyses.[37] A modified PH regression model then provided estimates of log hazard ratios with robust standard errors.[38]

To investigate shape of relationships, exposure variables were divided into fifths based on the overall standardised distribution across studies. The hazard or odds ratios in each fifth, compared to the lowest group, were estimated using Cox PH regression or logistic regression in each study separately. These risk ratios were pooled across studies using multivariate random-effects meta-analysis,[39,40] and floated variances were estimated,[41,42] which were then plotted against the mean exposure level in each quantile group. Estimation of floated variances does not alter the risk ratio values, but ascribes an appropriate variance to the log of the risk ratio for each group, including even the reference group with a risk ratio of 1 (rather than having one group arbitrarily chosen to have a relative risk of 1 with no associated variation). This allows the values to be compared informatively (ie, with known variance) between any pair of exposure categories, rather than only between each exposure category and the arbitrarily chosen reference group.

To investigate confounding, adjustment was made progressively for increasing numbers of potential confounding factors. Use of simple linear terms for age at baseline was generally sufficient, but empirical comparisons were made of alternatives as sensitivity analyses (eg, adjustment or stratification by age categories at baseline, and inclusion of quadratic terms and interactions with other covariates, especially sex). Similar considerations applied to adjustment for other covariates. The change in the Wald χ^2 statistic provides an indication of the change in the evidence of association and/or increase in uncertainty following adjustment.[43,44]

Joint effects − Potential effect modifiers measured at the individual level, such as age or other risk markers, were assessed using within-study information.[45,46] A 2-stage procedure was adopted. Study-specific estimates of interaction terms δ_s for the potential effect modifier X_{si}, were estimated from model (3) and subsequently combined using random-effects meta-analysis, as in (2);

$$\log(h_{ski}(t \mid E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \gamma_s X_{si} + \delta_s E_{si} X_{si}. \qquad (3)$$

The overall interaction was then based only on within-study information. Model (3) has been extended to include adjustments for other confounders, and indeed their interactions with the exposure of interest; this has enabled investigation of whether a particular interaction was confounded by other main effects or interactions. Potential effect modifiers measured at the study level, such as population type or laboratory methods, were assessed entirely on between-study comparisons using random-effects meta-regression.[47] Using the estimates of β_s from (1), model (2) has been extended to include a study level covariate X_s by writing:

$$\begin{aligned} \hat{\beta}_s &= \beta_s + \varepsilon_s; \text{where } \varepsilon_s \sim N(0, s_s^2) \\ \beta_s &= \beta + \delta_B X_s + \eta_s; \text{where } \eta_s \sim N(0, \tau^2) \end{aligned} \qquad (4)$$

where δ_B is the between-study interaction term, with statistical significance assessed allowing for the residual between-study heterogeneity τ^2. So as to use the maximum available information, the overall interactions for baseline disease status (Figure 3 and eFigure 6) were calculated using random effects meta-analysis of both between- and within-study information.

Proportionality of hazards − This was evaluated in each study separately by including an interaction between the exposure and time, or by the commonly used diagnostic based on Schoenfeld residuals,[48] which gives a χ_1^2 statistic for each study. These independent χ_1^2 statistics were summed across the S studies, yielding a χ_S^2 statistic testing the hypothesis that PH holds in each study. However, because this approach is not a powerful test against the plausible alternative hypothesis that hazard ratios tend to decline with time in all studies, the interaction terms between the exposure and time were pooled over studies using random-effects meta-analysis. This provided an "average" interaction term and corresponding test statistic.

Heterogeneity − In addition to the standard χ^2 test for heterogeneity,[49] the impact of heterogeneity was expressed in terms of I^2, the percentage of variance in the estimated log hazard ratios from each study that is attributable to between-study variation as opposed to sampling variation.[50]

Assessment of cross-sectional correlates − Unadjusted Pearson correlation coefficients were pooled across studies by random effects meta-analysis of Fisher's Z transformation of cohort- and sex-specific correlation coefficients.[51] Associations of exposure variables with various characteristics were then assessed using a linear mixed model that included a study-level random gradient for the relationship between the correlate and exposure of interest, but a fixed constant for each study. The main effect of cohort was modelled as a separate fixed effect. Continuous variables were divided into tenths based on the overall distribution in males and females combined, allowing assessment of shape of associations without imposing *a priori* any particular shape. Natural logarithms were used to achieve approximately symmetrical distributions for positively skewed variables. Categorical variables were modelled similarly to the risk-factor tenths, except dummy variables were also used in the random effects equation since there was no natural monotonic ordering of the categories. From each fitted mixed model, overall adjusted means and 95% CI by sex within tenths of continuous markers (or within fifths if appropriate), or category for categorical variables, were obtained. These adjusted mean values were used to assess the shape of the association by plotting the mean (95% CI) of the exposure variable against the mean marker value within each quantile. An inverse-variance weighted polynomial was superimposed across the adjusted means to assess whether the overall association was consistent with a linear or a quadratic shape.

Assessment of measurement error and within-person variation − Measurement error and within-person variability in an exposure variable can cause any association of disease with the current usual level of the exposure to be underestimated.[52-54] The degree of underestimation, or regression dilution bias,[52,53] was quantified by regressing serial measurements of the exposure on baseline exposure and confounder values to provide a regression dilution ratio (RDR).[55] Available individual data shared with the Lp-PLA_2 Studies Collaboration was supplemented by tabular data sought from investigators. A combined estimate of the within-person variability of Lp-PLA_2 could not be made reliably because results from different studies were widely divergent.

Censoring of outcomes − For participants who had multiple events (eg, two CHD events at separate time points, or a CHD event followed by another type of event such as a stroke or death from cancer), analyses in the Lp-PLA_2 Studies Collaboration focused on first events only.[33] Thus, in an analysis of CHD events, participants were followed until their first CHD event, or censored at the time of other non-fatal cardiovascular events, such as stroke, or death from other causes. Individuals were not censored at the time of cardiovascular investigations or interventions, such as angiography or coronary bypass operations, or at the diagnosis of angina. The rationale for this was that major cardiovascular events, such as non-fatal MI or stroke, may disrupt the association between baseline risk factors and subsequent disease risk. The incidence of angina and coronary interventions was, however, not recorded reliably enough in sufficient studies to consider censoring for them. The potential biases that arise through these decisions on censoring were addressed through sensitivity analyses and by implementing alternative censoring criteria. In general, such changes had only minimal effects.

eAppendix 3. Potential bias from use of calculated LDL cholesterol in adjusted regression models

Because direct measurement of low density lipoprotein cholesterol (LDL-C) has been relatively uncommon in long-term prospective studies, most studies have tended to use the Friedewald equation[56] to estimate LDL-C values from the measured concentrations of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglycerides (divided by a constant):

$$\text{Calculated LDL-C} = \text{TC} - \text{HDL-C} - (\text{triglycerides}/2.2) \quad (1)$$

where triglycerides/2.2 approximates the concentration of cholesterol carried in very low density lipoprotein (VLDL-C) when the units of measurement are mmol/l (if mg/dl are used, the constant is 5.0).

Non-HDL-C (calculated as the difference between TC and HDL-C) can be substituted into equation 1:

$$\text{Calculated LDL-C} = \text{non-HDL-C} - (\text{triglycerides}/2.2) \quad (2)$$

As a consequence, any regression model (eg, Cox proportional hazards model for survival data, or logistic regression model for case-control data) that concomitantly includes calculated LDL-C, HDL-C and triglycerides, is simply a mathematical rearrangement of a model that includes non-HDL-C, HDL-C and triglycerides, as shown below.

Consider a survival model for the log hazard ratio (HR) including non-HDL-C, HDL-C and triglycerides (TG), where the mutually adjusted coefficients for each term are given by β_1, β_2 and β_3, respectively:

$$\text{logHR} = \beta_1 \text{ non-HDL-C} + \beta_2 \text{ HDL-C} + \beta_3 \text{ TG} \quad (3)$$

Adding and subtracting $(\beta_1/2.2)$ TG and simplifying yields:

$$\text{logHR} = \beta_1 \text{ non-HDL-C} + \beta_2 \text{ HDL-C} + \beta_3 \text{ TG} + (\beta_1/2.2 - \beta_1/2.2) \text{ TG}$$

$$= \beta_1 (\text{non-HDL-C} - \text{TG}/2.2) + \beta_2 \text{ HDL-C} + (\beta_3 + \beta_1/2.2) \text{ TG}$$

Substituting calculated LDL-C for (non-HDL-C – TG/2.2) as in equation 2 gives:

$$\text{logHR} = \beta_1 \text{ calculated LDL-C} + \beta_2 \text{ HDL-C} + (\beta_3 + \beta_1/2.2) \text{ TG} \quad (4)$$

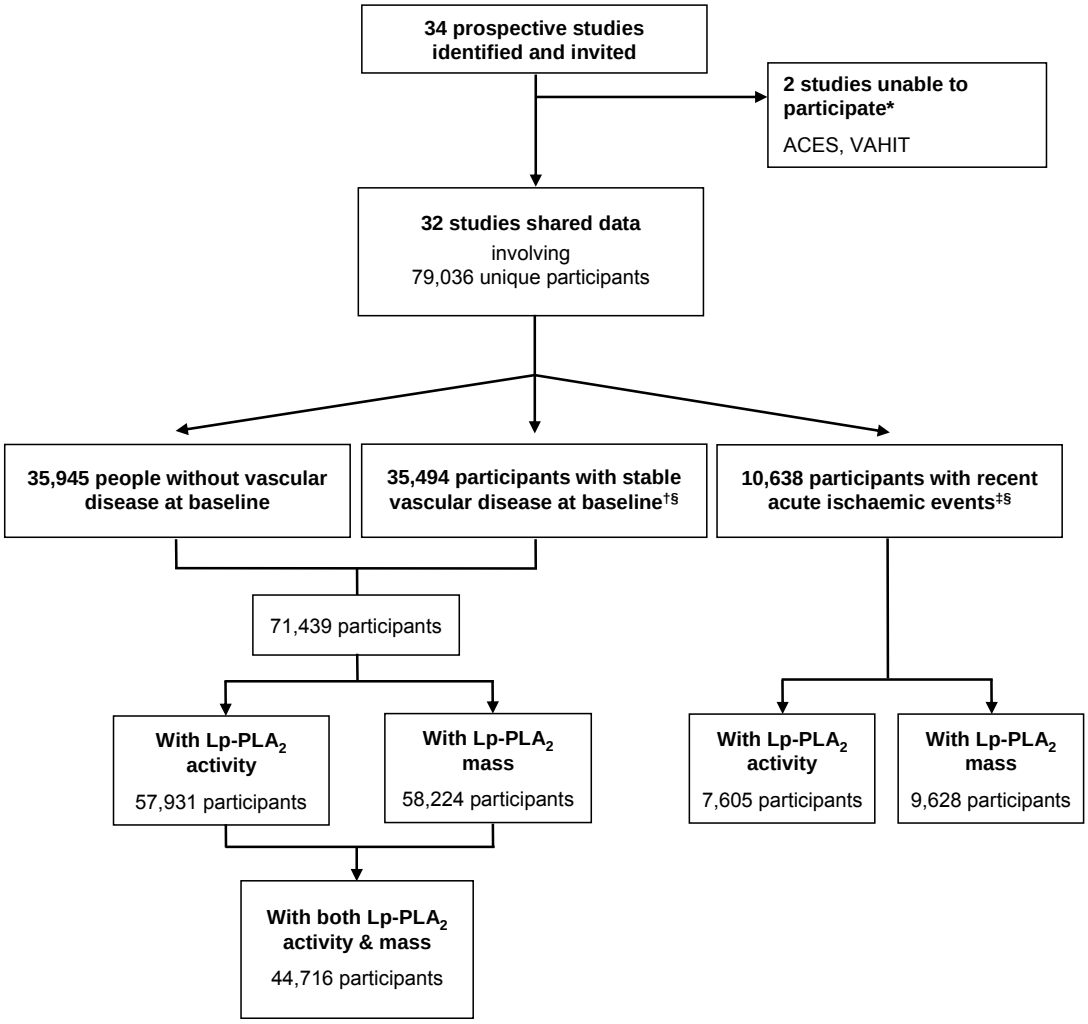
Comparing equations 3 and 4 demonstrates that:

- the calculated LDL-C parameter (β_1 in equation 4) equals the non-HDL-C parameter (β_1 in equation 3) in any model that also includes HDL-C and triglycerides. Indeed, any of the coefficients in equation 4 can be calculated from those in equation 3, should the need arise.

- when calculated LDL-C, HDL-C and triglycerides are included in the same model (equation 4), the coefficient for triglycerides is biased by $\beta_1/2.2$ (or $\beta_1/5.0$ if mg/dl are used) compared to equation 3. This means that even if triglycerides concentration was not associated with the outcome of interest in equation 3 (ie. $\beta_3 = 0$), then it would appear to have an association of $(\beta_1/2.2)$ when adjusted for calculated LDL-C and HDL-C in equation 4.

In the current LSC analyses, $\log_e$ triglycerides concentration has been used rather than triglycerides concentration, but a similar bias as described above for triglycerides concentration applies with use of calculated LDL-C. Hence, non-HDL-C concentration has been used in the current report rather than calculated LDL-C.

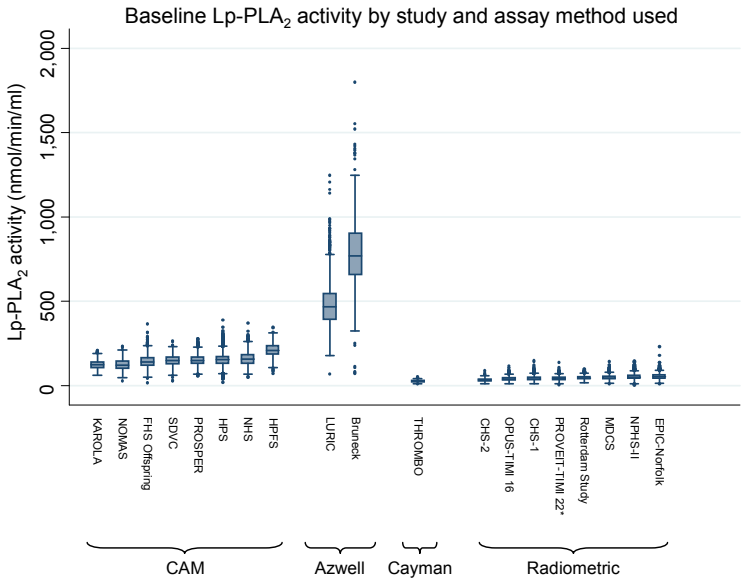
eFigure 1. Flow diagram of available data



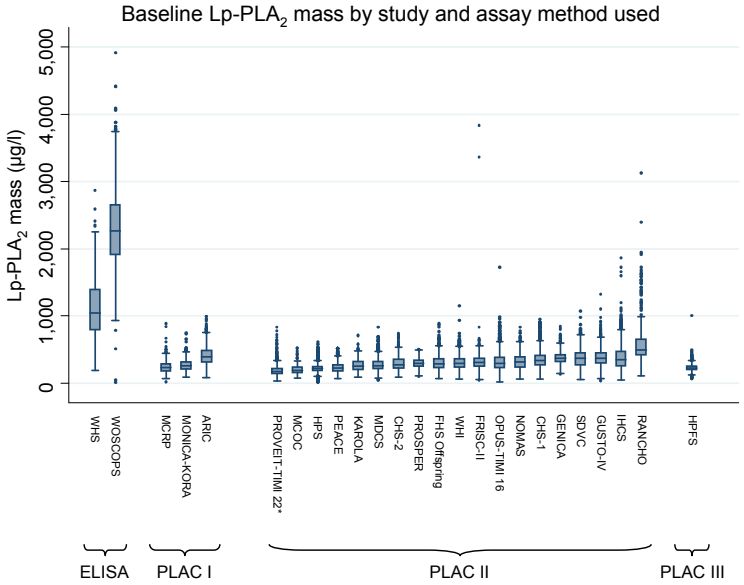
Numbers represent the maximum available information on Lp-PLA_2 regardless of the availability of other recorded covariates.

* These studies constitute only around 5% of relevant incident vascular outcomes in known studies
† Stable vascular disease was defined as diagnosis more than 30 days prior to baseline of any of the following: myocardial infarction [MI], angina, other CHD, stroke [including transient ischemic attack], peripheral vascular disease or coronary surgery, including revascularizations.
‡ Patients with recent acute ischaemic events were defined as those in which Lp-PLA_2 was measured in blood samples taken no more than 30 days after an index cardiovascular event had occurred (ie. MI, angina, CHD, any stroke, TIA, or coronary surgery including revascularizations).
§ The PROVEIT-TIMI 22 study provided data at two time points: at baseline survey from 3621 patients with recent acute ischaemic events, and 30 days later from 3041 of these patients who had survived event-free. Since participants with recent acute ischaemic events are always analysed separately from those with stable vascular disease, these 3041 participants have not been double counted.

eFigure 2. Box plots for baseline levels of Lp-PLA$_2$ activity and mass by study



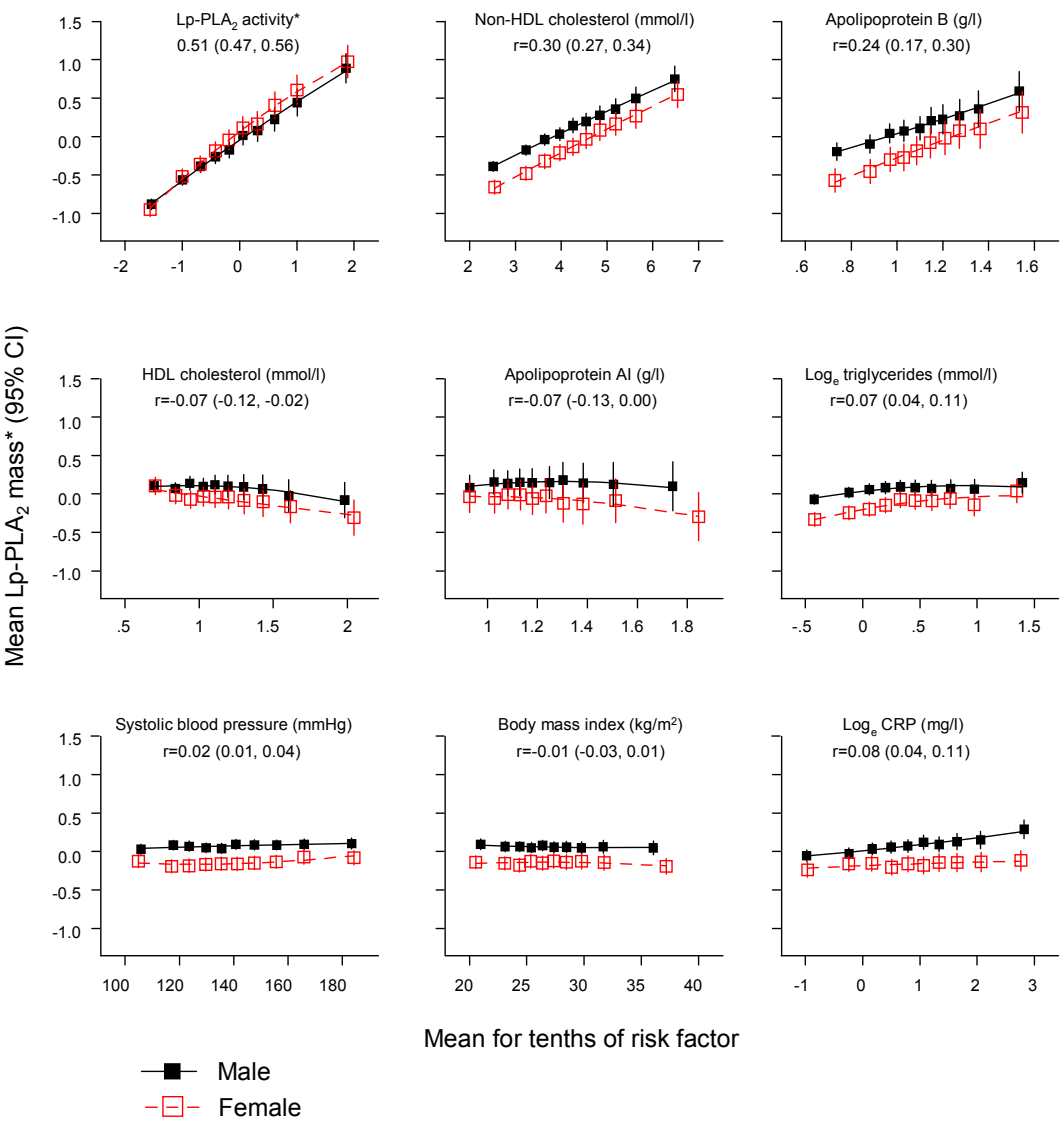
Pooled mean (SD) Lp-PLA$_2$ activity levels were: 151 (32) nmol/min/ml in studies that used CAM colorimetric assays; 629 (141) nmol/min/ml in studies that used Azwell colorimetric assays; 26 (6) nmol/min/ml in the study that used a Cayman colorimetric assay; and 42 (14) nmol/min/ml in studies that used radiometric assays.
Meta-regression for differences in mean levels across studies using different assay methods, p<0.0001 (excluding the two studies that used the Azwell assay, p<0.0001)



Pooled mean (SD) Lp-PLA$_2$ mass levels were: 1714 (547) µg/l in studies that used in-house ELISA; 305 (119) µg/l in studies that used PLAC I; 312 (95) µg/l in studies that used PLAC II; and 231 (53) µg/l in the study that used PLAC III.
Meta-regression for differences in mean levels across studies using different assay methods, p=0.0098 (excluding the two studies that used in-house ELISA, p=0.8092)

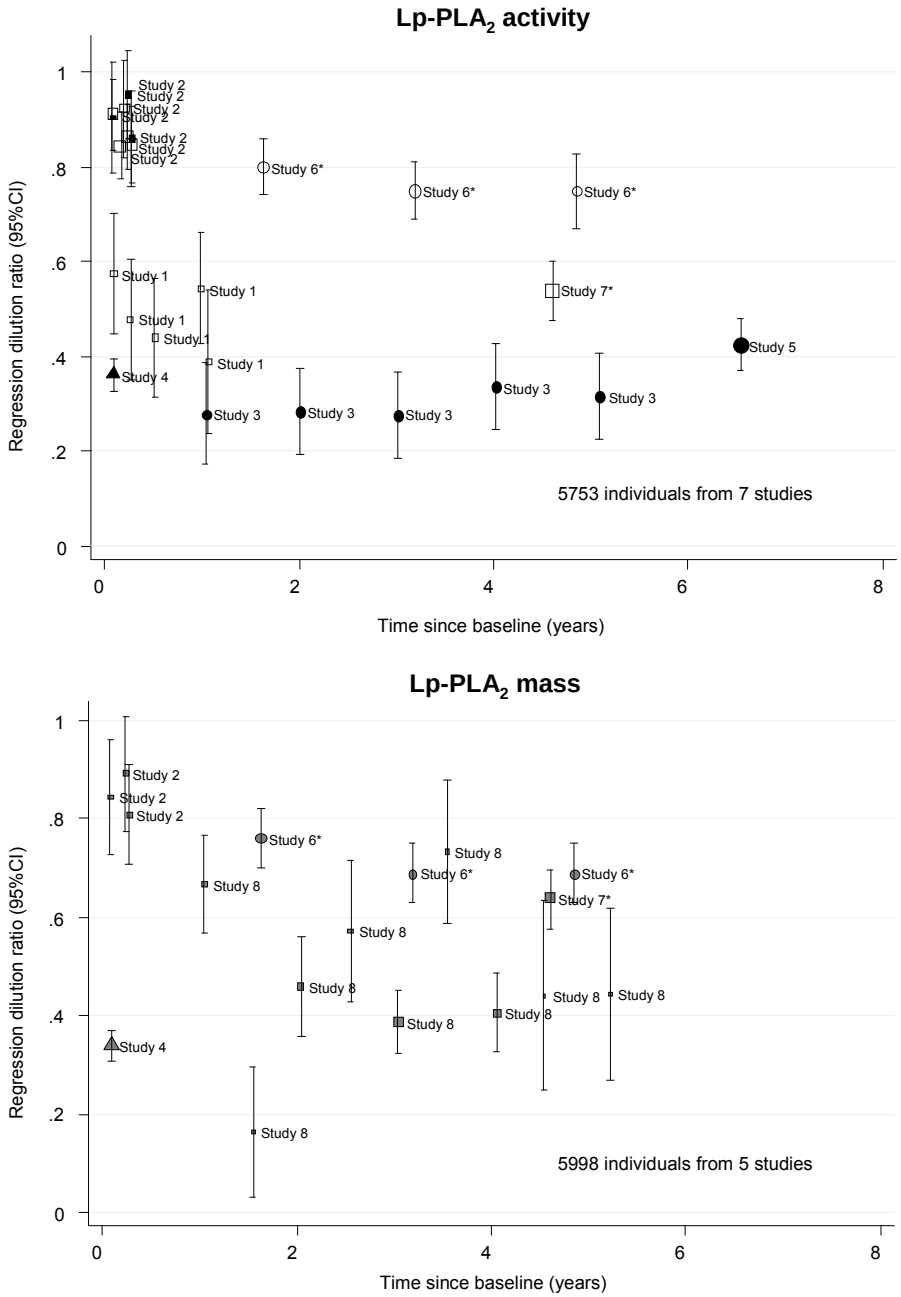
* Shown for PROVEIT-TIMI 22 study baseline survey. Median (inter-quartile range) for the 30 day resurvey were similar: 34 (26-43) for Lp-PLA$_2$ activity and 134 (95-183) for Lp-PLA$_2$ mass.

eFigure 3. Cross-sectional associations of Lp-PLA$_2$ mass



The numbers of participants included in each analysis are shown in **Table 1**.
Error bars represent the 95% CIs. r=Pearson's partial correlation coefficient (95% CI) adjusted for age, sex, history of diabetes and baseline history of vascular disease.
* Lp-PLA$_2$ activity and mass were standardised to a mean (SD) of 0.00 (1.00) in each study (see methods).

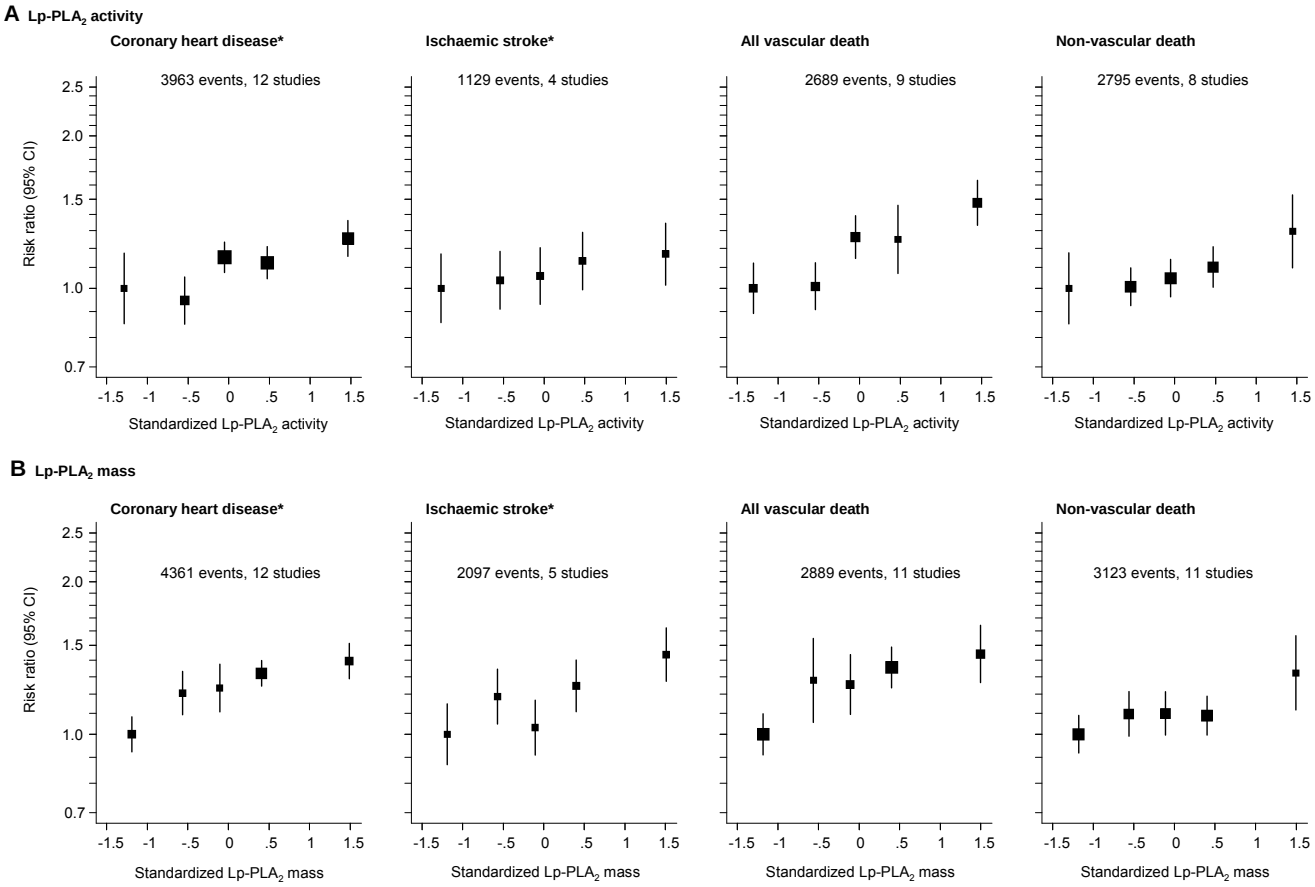
eFigure 4. Within-person variability in Lp-PLA$_2$ activity and mass (age and sex adjusted regression dilution ratios by study and time of repeat)



* Tabular data provided by investigators

Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the regression dilution ratios. Further information on the studies contributing to this figure is available on request.

eFigure 5. Adjusted risk ratios for coronary heart disease, ischaemic stroke and death due to vascular and nonvascular causes by fifths of Lp-PLA$_2$ activity or mass at baseline

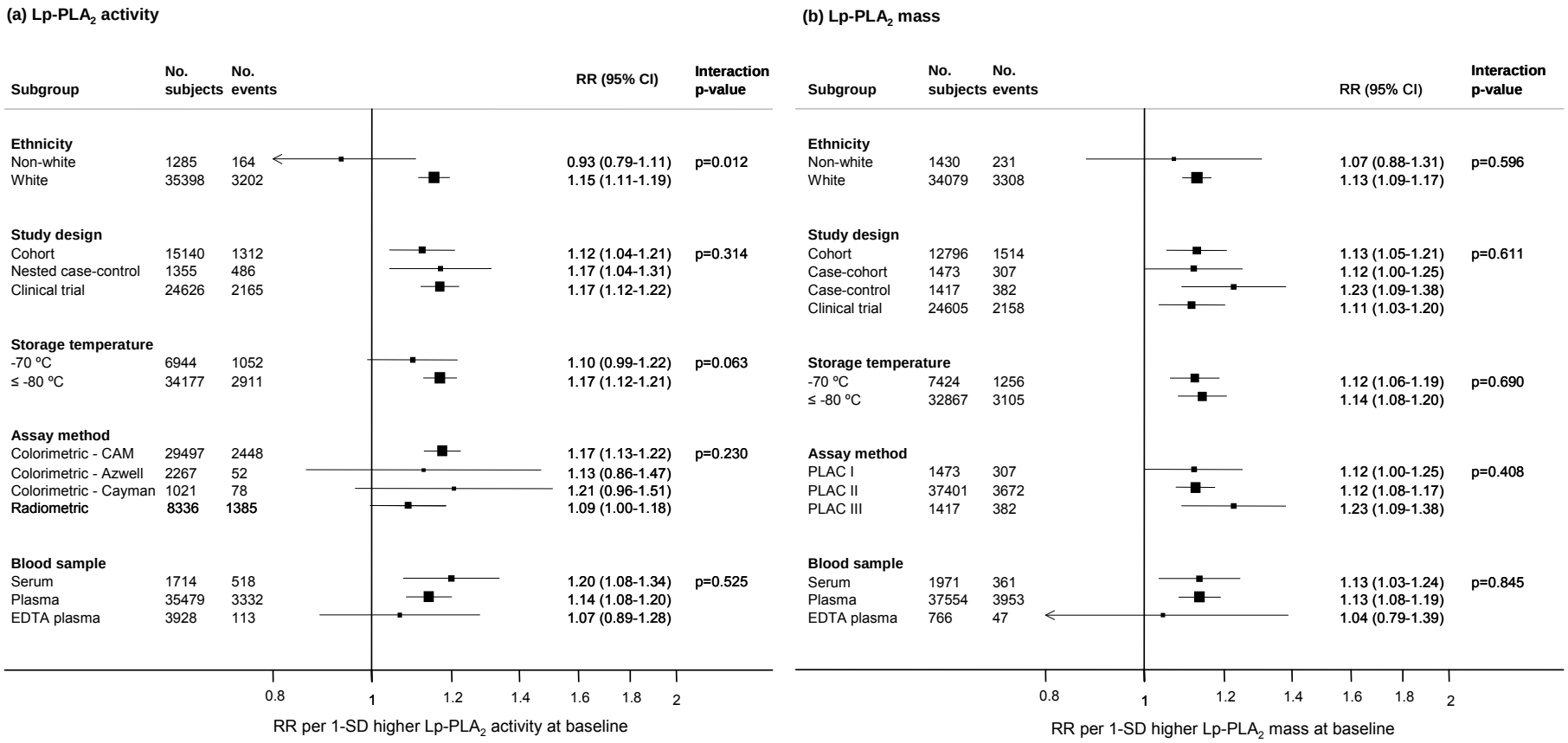


Risk ratios were adjusted for the nonlipid and lipid risk factors described in **Table 2**. Data are shown for the participants who were initially healthy or had a history of stable vascular disease at baseline only. One unit on the standardized scale is equal to one standard deviation on the untransformed scale. Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios

* Fatal and non-fatal events.

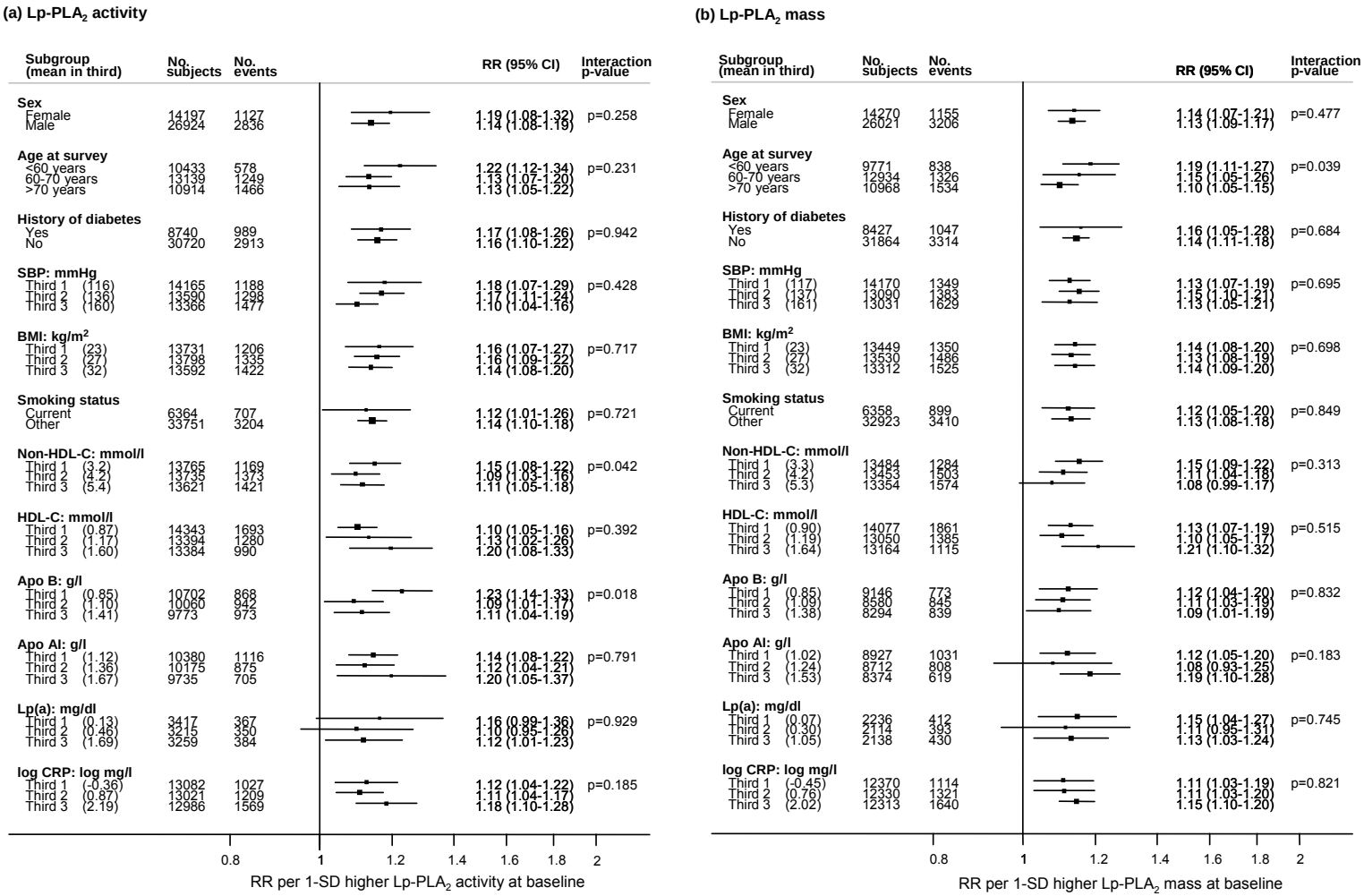
† Due to the lower number of studies and events involved, analyses of ischaemic stroke used a fixed-effect model for multivariate meta-analysis of study-specific risk ratios.

eFigure 6a. Adjusted risk ratios for coronary heart disease per 1-SD higher Lp-PLA$_2$ activity or mass at baseline grouped by various study-level characteristics



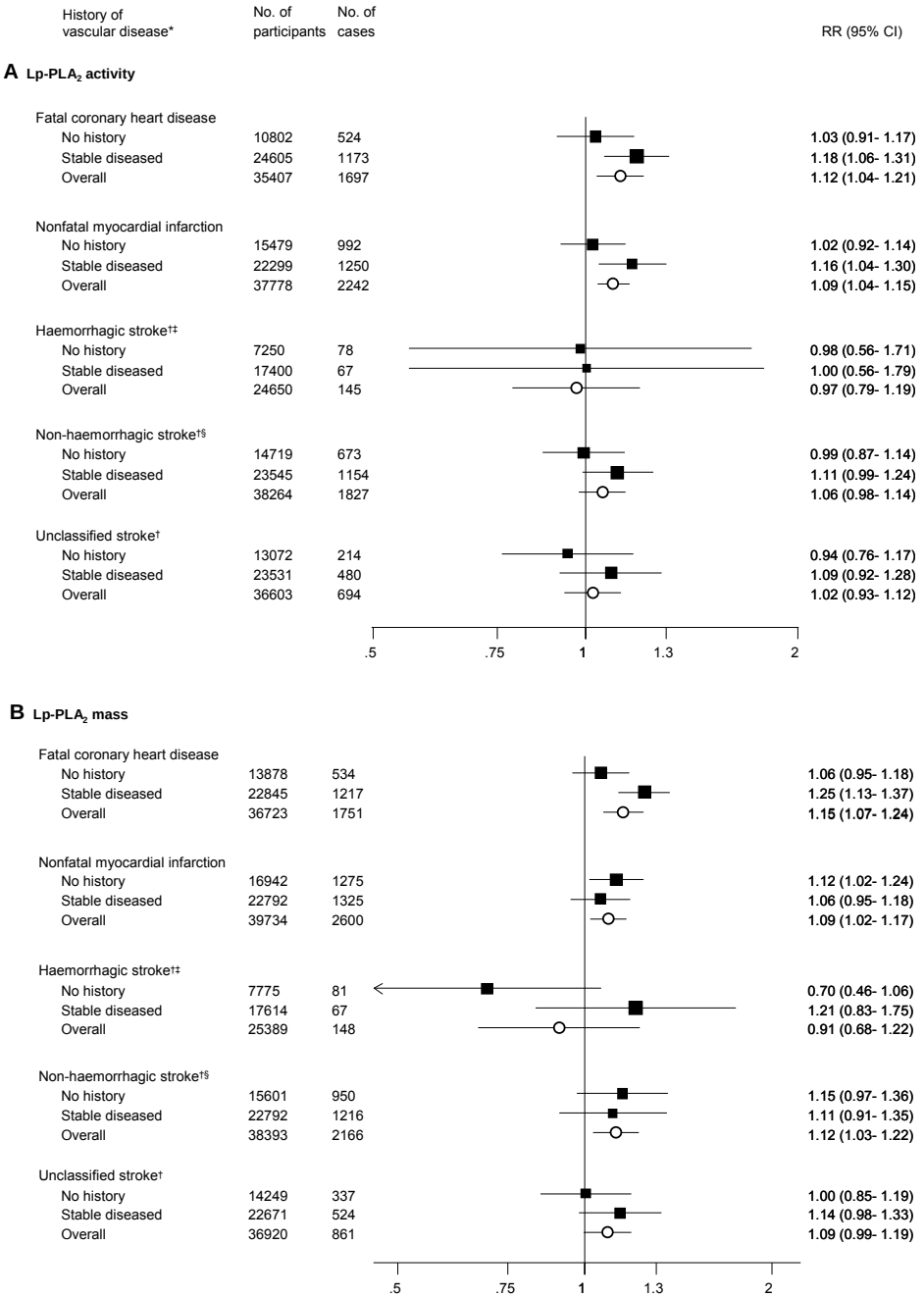
Risk ratios were adjusted for the nonlipid and lipid risk factors described in **Table 2**. Studies with fewer than 3 events per stratum were excluded. Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios.

eFigure 6b. Adjusted risk ratios for coronary heart disease per 1-SD higher Lp-PLA$_2$ activity or mass at baseline grouped by various individual-level characteristics



Risk ratios were adjusted for the nonlipid and lipid risk factors described in **Table 2**. Studies with fewer than 3 events per stratum were excluded. Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios.

eFigure 7. Adjusted risk ratios for coronary death, non-fatal myocardial infarction and stroke sub-types per 1-SD higher Lp-PLA$_2$ activity or mass at baseline



Risk ratios were adjusted for the nonlipid and lipid risk factors described in **Table 2** (except for the analyses of haemorrhagic stroke, which due to limited data, could not adjust for body mass index or smoking status). There were no significant differences in risk ratios between people with and without a history of stable vascular disease at baseline (p>0.10). Error bars represent the 95% CIs.

* Diagnosis more than 30 days prior to baseline of myocardial infarction, angina, other coronary heart disease, stroke [including transient ischaemic attack], peripheral vascular disease or coronary surgery [including revascularizations]).

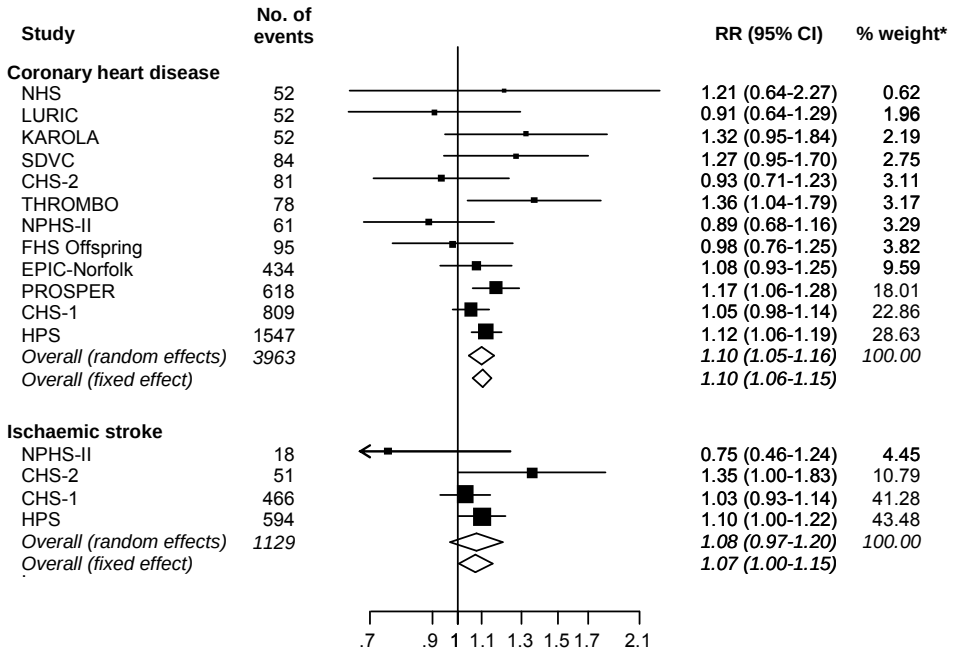
† Fatal and non-fatal events.

‡ Not adjusted for body mass index or smoking status.

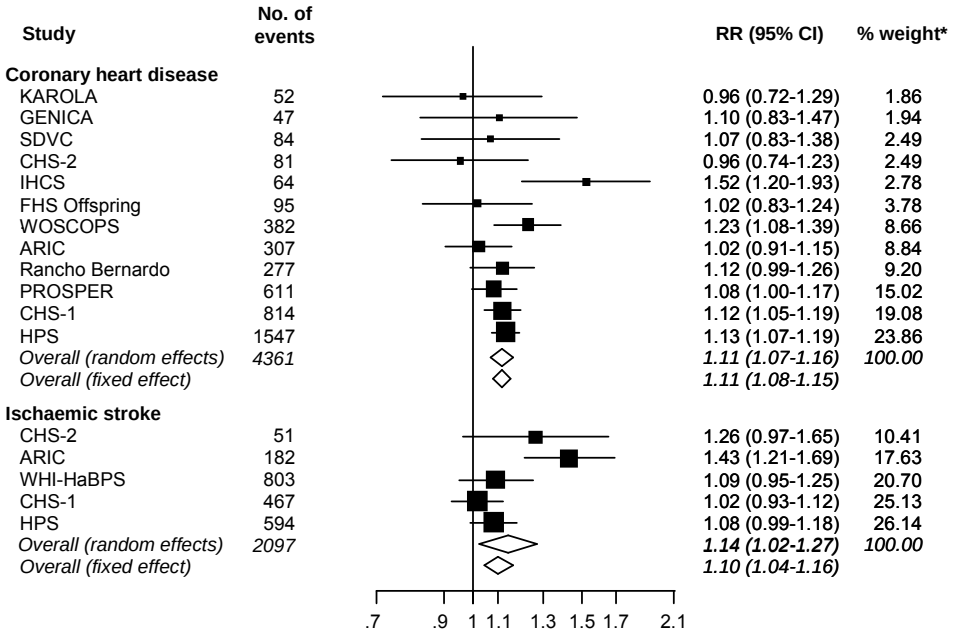
§ Defined as the aggregate of ischaemic and unclassified stroke

eFigure 8. Study-specific adjusted risk ratios for coronary heart disease and ischaemic stroke per 1-SD higher Lp-PLA$_2$ activity or mass at baseline (corresponding to the most adjusted estimates provided in Table 2)

(a) Lp-PLA$_2$ activity

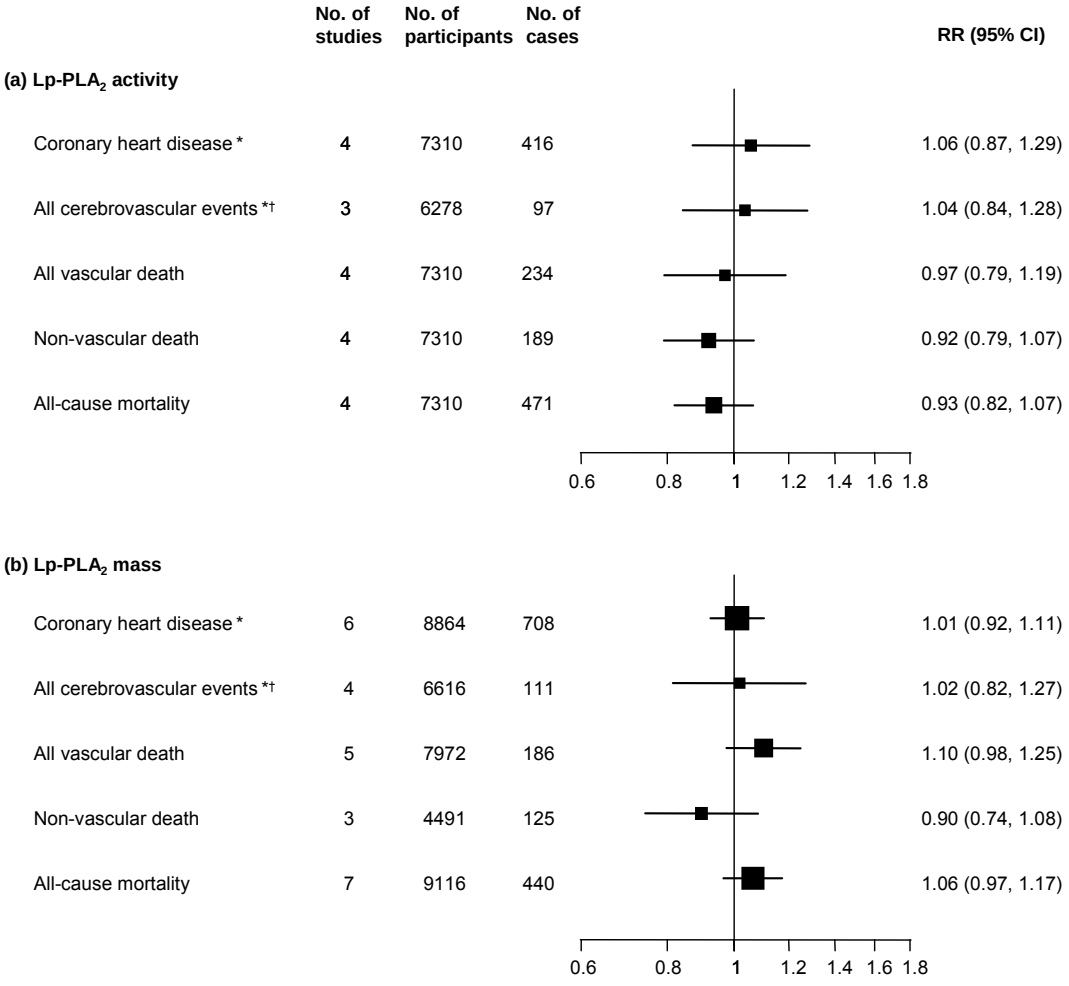


(b) Lp-PLA$_2$ mass



Data are shown for the participants who were initially healthy or had a history of stable vascular disease at baseline only. Studies contributing 10 or fewer outcomes to any particular analysis were excluded. Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios.
* Weights for random effects meta-analysis

eFigure 9. Risk ratios for incident vascular and nonvascular events in patients with acute ischemic syndromes per 1-SD higher Lp-PLA$_2$ activity or mass at baseline



Data are shown for patients with recent acute ischaemic events (defined as those in which Lp-PLA$_2$ was measured in blood samples taken no more than 30 days after an index cardiovascular event had occurred: ie, myocardial infarction, angina, CHD, any stroke, TIA, or coronary surgery including revascularizations). Risk ratios were adjusted for age, history of diabetes and type of index event, and stratified by sex and trial arm (as appropriate). Studies contributing 10 or fewer outcomes to any particular analysis were excluded. Error bars represent the 95% CIs. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios.
* Fatal and non-fatal events.
† Defined as any of ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, unclassified stroke or other cerebrovascular event.

eTable 1. Some baseline characteristics, blood handling and Lp-PLA$_2$ assay characteristics in studies contributing to the current analysis

Study [reference]	Location	Study design	Population setting	Fasting status at blood sampling / duration	Sample source	Time between blood collection and Lp-PLA$_2$ assay (years)	Sample state before analysis, storage temperature (°C)	Assay method	
								Lp-PLA$_2$ activity	Lp-PLA$_2$ mass
ARIC [1,2]	USA	C-Cohort	Household listings	Fasted/12hrs	plasma	10-14	Frozen, -80	-	PLAC I
Bruneck [3]	Italy	Cohort	Population register	Fasted/>8hrs	plasma	4	Frozen, -70	Colorimetric (Azwell)	-
CHS-1* [4]	USA	Cohort	Medicare lists	Fasted/8-12hrs	plasma	15	Frozen, -70	Radiometric	PLAC II
CHS-2* [4]	USA	Cohort	Medicare lists	Fasted/8-12hrs	plasma	15	Frozen, -70	Radiometric	PLAC II
EPIC-Norfolk [5]	UK	NCC	GP lists	Non-fasted	serum	NS	Frozen, -80	Radiometric	-
FHS Offspring [6]	USA	Cohort	FHS offspring & spouses	Fasted/8-12hrs	plasma	4-7	Frozen, -80	Colorimetric (CAM)	PLAC II
FRISC-II [7]	Multinational	RCT	ACS patients	Non-fasted	plasma	6-8	Frozen, -70	-	PLAC II
GENICA [8]	Italy	Cohort	Angiography patients	Fasted/12hrs	plasma	6-8	Frozen, -80	-	PLAC II
GUSTO-IV [7]	Multinational	RCT	ACS patients	Non-fasted	serum	4-5	Frozen, -70	-	PLAC II
HPFS [9]	USA	NCC	Occupational	Fasted/0-8hrs	plasma	12-13	Frozen, -130	Colorimetric (CAM)	PLAC III
HPS [10]	UK	RCT	High risk individuals	Non-fasted	plasma	9-12	Frozen, -100	Colorimetric (CAM)	PLAC II
IHCS [11]	USA	Cohort	Angiography patients	Fasted/NS	plasma	NS	Frozen, -80	-	PLAC II
KAROLA [12]	Germany	Cohort	CHD rehabilitation patients	Fasted/12hrs	plasma	5	Frozen, -80	Colorimetric (CAM)	PLAC II
LURIC [13]	Germany	Cohort	Angiography patients	Fasted/8hrs	plasma	5	Frozen, -80	Colorimetric (Azwell)	-
MCOC [14]	USA	Cohort	Acute MI patients	Non-fasted	plasma	2.5	Frozen, -70	-	PLAC II
MCRP [15]	USA	Cohort	Angiography patients	Fasted/12hrs	plasma	NS	Frozen, -70	-	PLAC I
MDCS [16,17]	Sweden	Cohort	Population register	Fasted/10hrs	plasma	8	Frozen, -80	Radiometric	PLAC II
MONICA-KORA [18]	Germany	Cohort	Population register	Non-fasted	plasma	NS	Frozen, -80	-	PLAC I
NHS [9]	USA	NCC	Occupational	Fasted/0-8hrs	plasma	15-17	Frozen, -130	Colorimetric (CAM)	-
NOMAS [19]	USA	Cohort	Acute stroke patients	Fasted/0-12hrs	serum	7-12	Frozen, -80	Colorimetric (CAM)	PLAC II
NPHS-II [20]	UK	Cohort	GP lists	Non-fasted	plasma	11-13.5	Frozen, -80	Radiometric	-
OPUS-TIMI 16 [21]	Multinational	RCT	ACS patients	Non-fasted	plasma	NS	Frozen, -70	Radiometric	PLAC II
PEACE [22]	Multinational	RCT	CAD patients	Non-fasted	plasma	NS	Frozen, -70	-	PLAC II
PROSPER [23]	UK	RCT	Primary care screening	Fasted/NS	plasma	4	Frozen, -80	Colorimetric (CAM)	PLAC II
PROVEIT TIMI 22 [21†]	Multinational	RCT	ACS patients / 30 day survivors†	Fasted/NS	plasma	NS	Frozen, -70	Radiometric	PLAC II
Rancho Bernardo Study [24]	USA	Cohort	Household listings	Fasted/12hrs	serum	17-20	Frozen, -70	-	PLAC II
Rotterdam Study [25]	Netherlands	C-Cohort	Population register	Non-fasted	plasma	NS	Frozen, -80	Radiometric	-
SDVC [26]	USA	Cohort	PAD patients	Fasted/0-24hrs	serum	11-15	Frozen, -70	Colorimetric (CAM)	PLAC II
THROMBO [27]	USA	Cohort	MI survivors	Fasted/12hrs	plasma	8	Frozen, -70	Colorimetric (Cayman)	-
WHI-HaBPS [28]	USA	NCC	WHI screenees	Fasted/12hrs	plasma	NS	Frozen, -70	-	PLAC II
WHS [39]	USA	NCC	Occupational	Non-fasted	plasma	6-7	Frozen, -130	-	ELISA
WOSCOPS [30]	UK	NCC	Heart screening clinic	Fasted/12hrs	plasma	8	Frozen, -80	-	ELISA

Study acronyms are explained in **eAppendix 1**. Key: ACS, acute coronary syndrome; C-Cohort, case-cohort; CAD, coronary artery disease; CHD, coronary heart disease; ELISA, enzyme-linked immunosorbent assay; MI, myocardial infarction; NCC, nested case-control study; NS, not stated; RCT, clinical trial.

* In the current analysis, the CHS was analysed as two separate studies (CHS-1 and CHS-2) stratified by ethnicity

† The PROVEIT-TIMI 22 study provided data at two time points. Data from the baseline survey was used in the combined analyses of patients with recent acute ischaemic events, while data from the 30 day resurvey was used in the analyses of patients with stable vascular disease. The same assay methods were used at both surveys.

eTable 2. Descriptive summaries by study of baseline characteristics of participants, follow-up time, and number of outcomes contributed.

Study	Total no. of people	Mean (SD) age at survey (yrs)	No. Male (%)	Mean (SD) Lp-PLA$_2$ levels: Activity (nmol/min/ml)	Mean (SD) Lp-PLA$_2$ levels: Mass (µg/l)	Median follow-up in years (5-95th centiles)	All CHD†	Non-fatal MI	CHD deaths	Ischaem. stroke†	Haem. stroke†	Unclass. stroke†	Other vascular deaths	All vascular deaths	Cancer deaths	Non-cancer non-vascular deaths	Unclass. deaths	All-cause mortality
Case-cohort studies																		
ARIC	1476	59 (6)	862 (58)	-	404 (142)	10.6 (1.5-12.7)	307	256	51	182	4*	2*	0	79	54	25	1*	159
Rotterdam study	1996	69 (9)	792 (40)	45 (12)	-	6.2 (1.6-8.3)	150	142	8*	105	6*	20	0	117	92	60	34	303
Nested case-control studies‡																		
EPIC Norfolk	3374	65 (8)	2136 (63)	52 (16)	-	7.6 (3.4-9.4)	491	261	230	0	0	0	0	0	0	0	0	0
HPFS	1353	64 (9)	1353 (100)	210 (38)	231 (53)	10.7 (2.3-11.5)	411	336	75	0	0	0	0	0	0	0	0	0
NHS	1289	59 (7)	0 (0)	159 (40)	-	15.1 (2.7-15.9)	426	360	66	0	0	0	0	0	0	0	0	0
WHI-HaBPS	1864	69 (6)	0 (0)	-	303 (93)	6.7 (1.1-9.3)	0	0	0	877	0	0	0	0	0	0	0	0
WHS	246	61 (8)	0 (0)	-	1128 (495)	1.6 (0.1-3.5)	74	63	11	0	0	49	0	0	0	0	0	0
WOSCOPS	1557	57 (5)	1557 (100)	-	2300 (554)	4.7 (0.9-5.8)	382	306	76	0	0	0	0	0	0	0	0	0
Cohort studies																		
Bruneck	789	63 (11)	398 (50)	783 (204)	-	10.4 (2.4-10.4)	54	19	35	21	11	0	8*	57	53	53	0	163
CHS1	4862	73 (5)	2043 (42)	40 (13)	351 (119)	11.7 (1.9-12.9)	819	406	413	473	72	68	92	530	0	1086	1*	1617
CHS2	645	73 (5)	242 (38)	33 (10)	295 (101)	9.1 (1.5-9.5)	83	42	41	56	5*	15	8*	59	0	94	1*	154
FHS Offspring	3274	61 (9)	1525 (47)	143 (35)	300 (94)	6.2 (2.9-7.5)	96	86	10*	0	0	59	9*	19	83	50	6*	158
GENICA	912	63 (10)	676 (74)	-	375 (99)	3.7 (0.6-4.8)	52	33	19	0	0	21	37	61	0	32	14	107
IHCS	1485	63 (12)	1040 (70)	-	391 (195)	8.3 (0.5-9.4)	290	185	105	0	0	59	56	161	0	152	0	313
KAROLA	1051	59 (8)	892 (85)	122 (26)	267 (83)	4.6 (1.0-4.9)	58	34	24	1*	1*	31	2*	30	15	6*	0	51
LURIC	3299	63 (11)	2299 (70)	475 (121)	-	7.7 (1.4-7.7)	88	0	88	0	0	37	310	435	94	183	23	735
MCOC	252	67 (14)	151 (60)	-	205 (71)	1.5 (0.0-2.6)	0	0	0	0	0	0	0	0	0	0	46	46
MCRP	475	60 (11)	290 (61)	-	244 (93)	4.0 (1.9-4.4)	18	14	4*	0	0	8*	0	4*	0	10*	0	14
MDCS	5391	58 (6)	2231 (41)	45 (13)	270 (81)	10.2 (5.6-11.5)	192	160	32	147	4*	33	34	76	220	52	6*	354
MONICA-KORA	923	54 (6)	923 (100)	-	267 (84)	12.9 (3.4-13.4)	90	48	42	0	2*	2*	27	75	45	26	1*	147
NOMAS	399	68 (12)	183 (46)	123 (34)	331 (123)	0.5 (0.1-3.5)	19	11	8*	38	2*	25	19	41	15	33	28	117
NPHS-II	2416	56 (4)	2416 (100)	50 (16)	-	13.8 (4.7-15.4)	142	141	1*	29	3*	5*	3*	5*	1*	1*	0	7*
Rancho Bernardo	1514	71 (10)	852 (56)	-	551 (225)	12.1 (1.5-18.8)	280	110	170	8*	14	155	123	375	162	213	2*	752
SDVC	499	68 (9)	441 (88)	146 (33)	381 (151)	7.9 (1.0-11.0)	88	0	88	1*	2*	7*	50	151	59	82	8*	300
THROMBO	1030	59 (12)	779 (76)	26 (6)	-	1.9 (0.5-3.0)	79	55	24	0	0	0	0	24	0	0	0	24
Clinical trials																		
FRISC-II	1356	67 (10)	955 (70)	-	317 (156)	1.0 (0.0-1.2)	177	160	17	2*	2*	1*	3*	25	1*	1*	5*	32
GUSTO-IV	894	65 (11)	572 (64)	-	386 (145)	0.1 (0.0-0.1)	30	30	0	0	5*	1*	0	0	0	0	26	26
HPS	19047	64 (8)	14371 (75)	152 (32)	222 (52)	5.2 (1.6-6.6)	1550	841	709	597	62	250	531	1382	617	299	15	2313
OPUS-TIMI 16	2319	60 (11)	1699 (73)	39 (12)	318 (127)	0.6 (0.3-1.1)	92	87	5*	10*	3*	2*	27	32	0	11	6*	49
PEACE	3765	64 (8)	3053 (81)	-	231 (73)	7.2 (2.1-7.2)	210	210	0	0	0	66	114	114	0	150	0	264
PROSPER	5663	75 (3)	2729 (48)	149 (30)	296 (67)	3.2 (0.9-3.8)	619	456	163	0	0	245	30	220	182	75	0	477
PROVEIT-TIMI 22§	3621	58 (11)	2830 (78)	41 (12)	181 (72)	2.0 (0.2-2.6)	272	243	29	0	0	30	7*	36	21	16	10*	83
TOTAL	**79036**	**64 (10)**	**50290 (64)**	NA¶	NA¶	**5.6 (0.6-12.9)**	**7639**	**5095**	**2544**	**2547**	**198**	**1191**	**1490**	**4108**	**1714**	**2710**	**233**	**8765**

Study acronyms are explained in **eAppendix 1**. Key: CHD, coronary heart disease; Haem, haemorrhagic; Ischaem, ischaemic; MI, myocardial infarction; SD, standard deviation; Unclass, unclassified.

Footnote continued on next page.

* Studies contributing 10 or fewer outcomes to any particular analysis were excluded.
† Fatal and non-fatal events
‡ By design nested case-control studies of non-fatal vascular outcomes could not contribute to the analyses of vascular death or non-vascular death.
§ Data are shown for the baseline survey in ACS patients. Corresponding data from the 30-day resurvey were: 3041 patients, 2378 (78%) men, 36 (13) nmol/min/ml Lp-PLA_2 activity; 145 (66) μg/l Lp-PLA_2 mass; 199 CHD events (22 fatal, 177 nonfatal); 21 unclassified stroke (0 ischaemic or haemorrhagic); 4 other vascular deaths; 26 all vascular deaths; 17 cancer deaths; 16 non-cancer non-vascular deaths; 6 unclassified deaths; and 65 all cause deaths.
¶ Overall mean (SD) Lp-PLA_2 levels grouped according to assay method used are shown in the legend to **eFigure 2**.

eTable 3. Characterization of baseline and incident cardiovascular disease outcomes in studies contributing to the current analysis

	Disease assessed at baseline				Definition of incident outcomes						Classification of incident outcomes						
					Death	Nonfatal MI			Nonfatal stroke		MI			Stroke			
Study	**MI**	**Angina**	**Coronary revasc**	**Stroke**		**Clinical feature**	**ECG**	**Cardiac markers**	**Clinical feature**	**CT/MRI imaging**	**Definite**	**Probable**	**Silent**	**Ischemic**	**Hemorrhagic**	**SAH**	**Unclassified**
ARIC	++	++	++	+	**	✓	✓	✓	✓	✓	✓	✓NC	✓NC	✓	✓	✓	✓
Bruneck	++	++	++	+	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	0	0
CHS-1†	++	++	++	+	**	✓	✓	✓	✓	✓	✓	✓NC	✓NC	✓	✓	0	✓
CHS-2†	++	++	++	+	**	✓	✓	✓	✓	✓	✓	✓NC	✓NC	✓	✓	0	✓
EPIC-Norfolk	+	–	–	+	*	✓	✓	✓	NA	NA	✓	0	0	✓NC	✓NC	✓NC	✓NC
FHS Offspring	++	++	–	+	**	✓	✓	✓	✓	✓	✓	0	✓NC	✓NC	✓NC	✓NC	✓
FRISC II	++	++	++	+	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	0	✓
GENICA	++	++	++	+	**	✓	✓	✓	NA	NA	✓	0	0	0	0	0	✓
GUSTO IV	++	++	++	+	**	✓	✓	✓	✓	✓	✓	0		✓NC	✓	0	✓
HPFS	+	+	+	+	**	✓	✓	✓	NA	NA	✓	✓NC	0	0	0	0	✓NC
HPS	+	+	+	+	**	✓	✓	✓	✓	✓	✓	✓NC	0	✓	✓	✓	✓
IHCS	++	++	++NC	+	*	✓	✓	✓	NA	NA	✓	0	0	0	0	0	✓
KAROLA	++	–	++	+	*	✓	✓	✓	✓	✓	✓	0	0	✓	✓	0	✓
LURIC	++	++	++NC	+	*	NA	NA	NA	NA	NA	✓	0	0	0	0	0	✓
MCOC	++	–	–	–	*	NA	NA	NA	NA	NA	0	0	0	0	0	0	0
MCRP	++	++	++NC	–	**	✓	✓	✓	✓	✓	✓	0	0	✓NC	✓NC	✓NC	✓
MDCS	+	++	–	+	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	✓	✓
MONICA-KORA	+	+NC	–	+	**	✓	✓	✓	NA	NA	✓	✓NC	0	✓	✓	✓	✓
NHS	+	+	+		**	✓	✓	✓	NA	NA	✓	✓NC	0	0	0	0	0
NOMAS	++	++	++	++	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	✓	✓
NPHS-II	++	++	++ NC		**	✓	✓	✓	✓	✓	✓	✓NC	✓NC	✓	✓	✓	✓
OPUS-TIMI 16	++	++	–	+	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	0	✓
PEACE	++	++	++	+	**	✓	✓	✓	✓	✓	✓	0	0	0	0	0	✓
PROSPER	++	++	++		**	✓	✓	✓	✓	✓	✓	0	0	✓NC	✓NC	✓NC	✓
PROVEIT-TIMI 22‡	++	++	++	+	**	✓	✓	✓	✓	✓	✓	0	0	✓NC	✓NC	0	✓
Rancho Bernardo	++	++	++	+	*	✓	✓	✓	✓	✓	✓	0	0	✓	✓	✓	✓
Rotterdam Study	++	++NC	++	+	**	✓	✓	✓	✓	✓	✓	0	0	✓	✓	✓	✓
SDVC	+	+	+	+	*	NA	NA	NA	NA	NA	✓	0	0	✓	✓	✓	✓
THROMBO	++	–	++	–	**	✓	✓	✓	NA	NA	✓	0	0	0	0	0	0
WHI-HaBPS	++	++	++	+	*	NA	NA	NA	✓	✓	0	0	0	✓	0	0	0
WHS	+	+	+	+	**	✓	✓	✓	✓	✓	✓	0	0	0	0	0	✓
WOSCOPS	++	++	++ NC	+	**	✓	✓	✓	NA	NA	✓	✓	✓NC	0	0	0	0

Study acronyms are explained in **eAppendix 1**

† The CHS was analysed as two separate studies stratified by ethnicity

‡ The PROVEIT-TIMI 22 study baseline and 30 day surveys used the same methods.

–: Not recorded; +: Self-report only; ++: Self-report supplemented by objective criteria (e.g., Electrocardiogram, Physical examination); * Death certificate only; ** Death certificate supplemented by medical record; 0: Feature not included in criteria; ✓: Feature included in criteria; SAH: Subarachnoid haemorrhage; NS: Not stated; NC = reportedly measured but data not contributed to the LSC; NA = not applicable, where cohorts contributed data on fatal outcomes only

eTable 4. Risk ratios for coronary heart disease per 1-SD higher Lp-PLA$_2$ activity or mass at baseline, with progressive adjustment for baseline levels of different groups of potential confounders

Subset / Degree of adjustment	Lp-PLA$_2$ activity			Lp-PLA$_2$ mass		
	RR (95%CI)	Wald χ^2_1	I^2 (95% CI)	RR (95%CI)	Wald χ^2_1	I^2 (95% CI)
Both Lp-PLA$_2$ markers	**3278 events, 34762 participants, 7 studies**			**3278 events, 34762 participants, 7 studies**		
Minimally adjusted*	1.16 (1.08-1.24)	18	58 (2-82)	1.14 (1.10-1.18)	61	0 (0-71)
plus nonlipid risk factors†	1.15 (1.08-1.24)	17	58 (3-82)	1.13 (1.09-1.17)	52	0 (0-71)
plus conventional lipids‡	1.11 (1.05-1.16)	17	14 (0-75)	1.11 (1.07-1.15)	33	0 (0-71)
plus Lp-PLA$_2$ mass	1.07 (1.00-1.14)	4	28 (0-69)	-	-	-
plus Lp-PLA$_2$ activity	-	-	-	1.08 (1.04-1.12)	14	0 (0-71)
Apolipoproteins	**2771 events, 30844 participants, 6 studies**			**2455 events, 26005 participants, 3 studies**		
Minimally adjusted*	1.16 (1.09-1.24)	23	36 (0-75)	1.14 (1.08-1.20)	24	34 (0-78)
plus nonlipid risk factors†	1.15 (1.08-1.24)	17	45 (0-78)	1.13 (1.09-1.18)	36	5 (0-90)
plus apolipoprotein B	1.12 (1.04-1.20)	9	43 (0-78)	1.11 (1.07-1.16)	27	0 (0-90)
plus apolipoprotein AI	1.10 (1.02-1.18)	6	38 (0-75)	1.12 (1.07-1.16)	29	0 (0-90)
Apolipoproteins & conventional lipids	**2783 events, 30523 participants, 7 studies**			**2457 events, 26020 participants, 3 studies**		
Minimally adjusted*	1.17 (1.12 - 1.21)	59	0 (0 to 71)	1.12 (1.07 - 1.18)	24	21 (0 to 92)
plus nonlipid risk factors†	1.18 (1.13 - 1.22)	64	0 (0 to 71)	1.13 (1.09 - 1.18)	35	7 (0 to 90)
plus conventional lipids‡	1.13 (1.07 - 1.19)	20	7 (0 to 73)	1.10 (1.05 - 1.16)	15	19 (0 to 92)
plus apolipoprotein B	1.12 (1.07 - 1.18)	20	5 (0 to 72)	1.10 (1.04 - 1.16)	11	34 (0 to 78)
Directly measured LDL cholesterol	**2262 events, 27873 participants, 4 studies**			**2921 events, 28807 participants, 6 studies**		
Minimally adjusted*	1.17 (1.12 - 1.22)	54	0 (0 to 85)	1.16 (1.09 - 1.23)	20	53 (0 to 81)
plus nonlipid risk factors†	1.18 (1.11 - 1.26)	28	27 (0 to 73)	1.16 (1.10 - 1.23)	25	45 (0 to 78)
plus LDL cholesterol	1.16 (1.11 - 1.21)	39	0 (0 to 85)	1.14 (1.07 - 1.21)	17	44 (0 to 78)
plus HDL cholesterol	1.13 (1.08 - 1.19)	26	0 (0 to 85)	1.14 (1.07 - 1.22)	15	50 (0 to 80)
C-reactive protein	**3805 events, 39089 participants, 12 studies**			**4075 events, 37013 participants, 11 studies**		
Minimally adjusted*	1.16 (1.10-1.22)	32	35 (0-67)	1.15 (1.11-1.19)	55	17 (0-58)
plus nonlipid risk factors†	1.15 (1.10-1.22)	29	38 (0-68)	1.14 (1.10-1.18)	47	18 (0-58)
plus conventional lipids‡	1.10 (1.05-1.16)	13	24 (0-61)	1.11 (1.06-1.16)	19	32 (0-66)
plus $\log_e$ C-reactive protein	1.11 (1.05-1.17)	15	26 (0-62)	1.09 (1.04-1.15)	14	34 (0-67)
Fibrinogen	**1200 events, 13672 participants, 7 studies**			**1359 events, 10054 participants, 4 studies**		
Minimally adjusted*	1.11 (1.01-1.22)	5	34 (0-72)	1.14 (1.08-1.21)	22	5 (0-85)
plus nonlipid risk factors†	1.10 (1.00-1.21)	4	32 (0-71)	1.13 (1.07-1.20)	18	7 (0-86)
plus conventional lipids‡	1.03 (0.92-1.16)	0	35 (0-73)	1.12 (1.04-1.20)	9	20 (0-88)
plus fibrinogen	1.05 (0.94-1.18)	1	34 (0-72)	1.12 (1.04-1.20)	9	18 (0-87)

Abbreviation: CI, confidence interval; SD, standard deviation; RR, risk ratio.
Analyses were restricted to participants with complete information within each subset. Studies contributing 10 or fewer outcomes to any particular analysis were excluded. The Wald χ^2_1 statistic indicates the significance of the accompanying risk ratio. The I^2 statistic estimates the percentage of heterogeneity in the study-specific risk ratios that can be accounted for by between-study differences and not chance.

* Adjusted for age and history of diabetes, and stratified by sex, baseline history of vascular disease and trial arm (as appropriate).
† Lipid-lowering drug use, systolic blood pressure, body mass index, and smoking status.
‡ Non-HDL cholesterol, HDL cholesterol, $\log_e$ triglycerides

eTable 5. Risk ratios for vascular deaths, nonvascular deaths, cancer deaths and non-vascular deaths not attributed to cancer per 1-SD higher Lp-PLA$_2$ activity or mass at baseline, with progressive adjustment for baseline levels of potential confounders

	Lp-PLA$_2$ activity			Lp-PLA$_2$ mass		
	RR (95%CI)	**Wald χ^2_1**	**I^2 (95% CI)**	**RR (95%CI)**	**Wald χ^2_1**	**I^2 (95% CI)**
All vascular deaths	**2689 events 38105 participants, 9 studies**			**2889 events 38874 participants, 11 studies**		
Minimally adjusted*	1.17 (1.12-1.23)	39	21 (0-62)	1.13 (1.04-1.22)	9	65 (34-82)
plus nonlipid risk factors†	1.17 (1.12-1.22)	43	13 (0-54)	1.12 (1.04-1.21)	8	63 (29-81)
plus conventional lipids‡	1.16 (1.09-1.24)	21	28 (0-66)	1.13 (1.05-1.22)	11	55 (11-77)
All nonvascular deaths	**2795 events 37084 participants, 8 studies**			**3123 events 38874 participants, 11 studies**		
Minimally adjusted*	1.05 (0.98-1.11)	2	45 (0-76)	1.07 (1.00-1.15)	4	64 (31-81)
plus nonlipid risk factors†	1.04 (0.98-1.10)	2	37 (0-72)	1.06 (0.99-1.14)	3	64 (31-81)
plus conventional lipids‡	1.10 (1.04-1.17)	11	26 (0-66)	1.10 (1.03-1.18)	8	53 (8-76)
Cancer deaths	**1004 events 31630 participants, 6 studies**			**1162 events 32309 participants, 7 studies**		
Minimally adjusted*	1.00 (0.92-1.09)	0	20 (0-64)	1.05 (0.93-1.18)	1	64 (19-84)
plus nonlipid risk factors†	1.00 (0.93-1.06)	0	0 (0-75)	1.03 (0.92-1.15)	0	60 (7-82)
plus conventional lipids‡	1.05 (0.97-1.14)	2	0 (0-75)	1.08 (0.98-1.18)	2	38 (0-74)
Non-cancer non-vascular deaths	**1785 events 36078 participants, 7 studies**			**1955 events 37821 participants, 10 studies**		
Minimally adjusted*	1.09 (0.99-1.19)	3	56 (0-81)	1.09 (1.00-1.18)	4	51 (0-76)
plus nonlipid risk factors†	1.09 (0.99-1.19)	3	53 (0-80)	1.08 (0.99-1.18)	3	54 (6-77)
plus conventional lipids‡	1.18 (1.07-1.30)	11	48 (0-78)	1.13 (1.04-1.23)	8	48 (0-75)

Abbreviation: CI, confidence interval; SD, standard deviation; RR, risk ratio.
Analyses were restricted to participants with complete information. Studies contributing 10 or fewer outcomes to any particular analysis were excluded. The Wald χ^2_1 statistic indicates the significance of the accompanying risk ratio. The I^2 statistic estimates the percentage of heterogeneity in the study-specific risk ratios that can be accounted for by between-study differences and not chance.

* Adjusted for age and history of diabetes, and stratified by sex, baseline history of vascular disease and trial arm (as appropriate).
† Lipid-lowering drug use, systolic blood pressure, body mass index, and smoking status.
‡ Non-HDL cholesterol, HDL cholesterol, $\log_e$ triglycerides

eTable 6. Risk ratios for vascular death per 1-SD higher Lp-PLA$_2$ mass at baseline, presented separately for people with and without a history of stable vascular disease at baseline and progressively adjusted for baseline levels of potential confounders

Degree of adjustment	No history* RR (95%CI)	Stable disease* RR (95%CI)
	763 events, 15672 participants, 5 studies	**2126 events, 23202 participants, 10 studies**
Minimally adjusted[†]	0.98(0.91-1.06)	1.28(1.21-1.35)
plus nonlipid risk factors[‡]	0.98(0.90-1.06)	1.29(1.22-1.37)
plus conventional lipids[§]	1.00 (0.92-1.09)	1.26 (1.19-1.34)

Abbreviation: CI, confidence interval; SD, standard deviation; RR, risk ratio.
Analyses were restricted to participants with complete information.
***** History of stable vascular disease at baseline (defined as a diagnosis more than 30 days prior to baseline of myocardial infarction, angina, other coronary heart disease, stroke [including transient ischaemic attack], peripheral vascular disease or coronary surgery [including revascularizations]).
[†] Adjusted for age and history of diabetes, and stratified by sex, baseline history of vascular disease and trial arm (as appropriate).
[‡] Lipid-lowering drug use, systolic blood pressure, body mass index, and smoking status.
[§] Non-HDL cholesterol, HDL cholesterol, $\log_e$ triglycerides

eTable 7. Summary of data available and associations with Lp-PLA$_2$ activity and mass levels at baseline survey in patients with acute ischemic syndromes

		Lp-PLA$_2$ activity Up to 7605 participants from 10 studies*			Lp-PLA$_2$ mass Up to 9628 participants from 13 studies*		
		n	Mean (SD) or %	Correlation† (95% CI)	n	Mean (SD) or %	Correlation† (95% CI)
Anthropometric markers							
Age at survey (years)		7604	62 (11)	-0.04 (-0.11, 0.04)	9627	63 (11)	0.01 (-0.04, 0.06)
Body mass index (kg/m^2)		7143	28 (5)	0.03 (0.01, 0.06)	8248	28 (5)	-0.01 (-0.06, 0.04)
Systolic blood pressure (mmHg)		7315	132 (20)	0.03 (-0.01, 0.07)	7081	133 (21)	0.01 (-0.01, 0.03)
Lipid markers							
Total cholesterol (mmol/l)		4804	5.1 (0.9)	0.56 (0.41, 0.68)	5849	5.1 (1.0)	0.25 (0.20, 0.29)
Non-HDL cholesterol (mmol/l)		4804	3.92 (0.91)	0.60 (0.44, 0.72)	5666	4.01 (0.98)	0.25 (0.20, 0.30)
HDL cholesterol (mmol/l)		5163	1.02 (0.28)	-0.09 (-0.14, -0.04)	6026	1.08 (0.31)	0.01 (-0.06, 0.08)
Log$_e$ triglycerides (mmol/l)		5171	0.53 (0.45)	0.25 (0.18, 0.32)	5895	0.53 (0.47)	0.02 (-0.06, 0.10)
LDL cholesterol (mmol/L)‡		1151	2.90 (0.85)	0.57 (0.52, 0.60)	372	2.91 (0.80)	0.23 (0.03, 0.41)
Apolipoprotein B (g/l)		1269	1.13 (0.27)	0.61 (0.48, 0.72)	433	1.09 (0.29)	0.30 (0.09, 0.49)
Apolipoprotein AI (g/l)		1269	1.24 (0.25)	-0.05 (-0.10, 0.01)	433	1.28 (0.27)	-0.03 (-0.12, 0.07)
Inflammatory markers							
Log$_e$ C-reactive protein (mg/l)		2232	1.54 (1.42)	-0.01 (-0.05, 0.03)	4114	1.23 (1.35)	0.07 (0.04, 0.10)
Fibrinogen (µmol/l)		2547	12 (4)	-0.06 (-0.11, -0.01)	3032	11 (3)	0.04 (0.00, 0.07)
Log$_e$ leucocyte count (x10^9/l)		6776	1.58 (0.31)	0.01 (-0.01, 0.04)	6940	1.61 (0.31)	0.03 (0.01, 0.05)
Categorical variables							
Sex:	Male	5671	75%	Ref	6987	73%	Ref
	Female	1934	25%	-0.12 (-0.16, -0.08)	2641	27%	-0.03 (-0.05, -0.01)
Ethnicity:	White	6762	89%	Ref	7329	90%	Ref
	Non-white	822	11%	-0.11 (-0.16, -0.07)	830	10%	-0.06 (-0.10, -0.02)
Smoking status:	Other	4897	66%	Ref	7003	74%	Ref
	Current	2541	34%	0.06 (0.04, 0.08)	2456	26%	0.05 (0.03, 0.07)
History of diabetes:	No	5920	78%	Ref	7828	82%	Ref
	Yes	1660	22%	-0.00 (-0.05, 0.04)	1773	18%	-0.01 (-0.05, 0.02)

Data are shown for the 10,638 patients with recent acute ischaemic events (defined as those in which Lp-PLA$_2$ was measured in blood samples taken no more than 30 days after an index cardiovascular event had occurred: ie, myocardial infarction, angina, CHD, any stroke, TIA, or coronary surgery including revascularizations). Risk ratios were adjusted for age, history of diabetes and type of index event, and stratified by sex and trial arm (as appropriate). Mean levels of Lp-PLA$_2$ by assay method are shown in **eFigure 2**.

***** One study contributed only one patient to these totals and is therefore not included in the analyses

† Partial correlation coefficient (or for categorical variables, the difference in standardised Lp-PLA$_2$ compared to the reference category) adjusted for age, sex, and baseline history of diabetes (as appropriate)

‡ Directly measured LDL cholesterol

References to supplementary materials

1. Ballantyne CM, Hoogeveen RC, Bang H et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2004; **109:** 837-42.

2. Ballantyne CM, Hoogeveen RC, Bang H et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med* 2005; **165:** 2479-84.

3. Kiechl S, Willeit J, Mayr M et al. Oxidized phospholipids, lipoprotein(a), lipoprotein-associated phospholipase A2 activity, and 10-year cardiovascular outcomes: prospective results from the Bruneck study. *Arterioscler Thromb Vasc Biol* 2007; **27:** 1788-95.

4. Jenny NS, Solomon C, Cushman M et al. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) and risk of cardiovascular disease in older adults: Results from the Cardiovascular Health Study. *Atherosclerosis* 2010; doi:10.1016/j.atherosclerosis.2009.09.021

5. Rana JS, Arsenault BJ, Després JP et al. Inflammatory biomarkers, physical activity, waist circumference, and risk of future coronary heart disease in healthy men and women. *Eur Heart J* 2010; doi:10.1093/eurheartj/ehp010

6. Schnabel R, Dupuis J, Larson MG et al. Clinical and genetic factors associated with lipoprotein-associated phospholipase A(2) in the Framingham Heart Study. Atherosclerosis 2009; **204:** 601-07.

7. Oldgren J, James SK, Siegbahn A, Wallentin L. Lipoprotein-associated phospholipase A2 does not predict mortality or new ischaemic events in acute coronary syndrome patients. *Eur Heart J* 2007; **28:** 699-704.

8. Pessina AC, Cesari M, Colonna S et al. Rationale and design of the "GENICA" study (Genetic and Environmental factors In Coronary Atherosclerosis): a study of the genetic factors playing a role in the development of coronary atherosclerosis. *High Blood Press Cardiovasc Prev* 2001; **9:** 83-85.

9. Hatoum IJ, Nelson JJ, Cook NR, Hu FB, Rimm EB. Dietary, lifestyle, and clinical predictors of lipoprotein-associated phospholipase A2 activity in individuals without coronary artery disease. *Am J Clin Nutr* 2010; doi:10.3945/ajcn.2009.28870

10. Heart Protection Study. Lipoprotein-associated phospholipase A_2 activity and mass in relation to major cardiovascular disease and nonvascular mortality. 2010 (submitted)

11. May HT, Horne BD, Anderson JL et al. Lipoprotein-associated phospholipase A2 independently predicts the angiographic diagnosis of coronary artery disease and coronary death. *Am Heart J* 2006; **152:** 997-1003.

12. Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. *Arterioscler Thromb Vasc Biol* 2006; **26:** 1586-93.

13. Winkler K, Hoffmann MM, Winkelmann BR et al. Lipoprotein-associated phospholipase A2 predicts 5-year cardiac mortality independently of established risk factors and adds prognostic information in patients with low and medium high-sensitivity C-reactive protein (the Ludwigshafen risk and cardiovascular health study). *Clin Chem* 2007; **53:** 1440-47.

14. Gerber Y, McConnell JP, Jaffe AS et al. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. *Arterioscler Thromb Vasc Bio.* 2006; **26:** 2517-22.

15. Brilakis ES, McConnell JP, Lennon RJ et al. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. *Eur Heart J* 2005; **26:** 137-44.

16. Persson M, Hedblad B, Nelson JJ, Berglund G. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. *Arterioscler Thromb Vasc Biol* 2007; **27:** 1411-16.

17. Persson M, Berglund G, Nelson JJ, Hedblad B. Lp-PLA2 activity and mass are associated with increased incidence of ischemic stroke: a population-based cohort study from Malmö, Sweden. *Atherosclerosis* 2008; **200:** 191-98.

18. Koenig W, Khuseyinova N, Lowel H, Trischler G, Meisinger C. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation* 2004; **110:** 1903-08.

19. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. *Arch Intern Med* 2006; **166:** 2073-80.

20. Drenos F, Talmud PJ, Casas JP et al. Integrated associations of genotypes with multiple blood biomarkers linked to coronary heart disease risk. *Hum Mol Genet* 2009; **18:** 2305-16.

21. O'Donoghue M, Morrow DA, Sabatine MS et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. *Circulation* 2006; **113:** 1745-52.

22. Sabatine MS, Morrow DA, O'Donoghue M et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol* 2007; **27:** 2463-69.

23. Caslake MJ, Packard CJ, Robertson M et al. Lipoprotein-associated phospholipase A(2), inflammatory biomarkers, and risk of cardiovascular disease in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Atherosclerosis* 2010; doi:10.1016/j.atherosclerosis.2009.10.041

24. Daniels LB, Laughlin GA, Sarno MJ et al. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. *J Am Coll Cardiol* 2008; **51:** 913-19.

25. Oei HH, van dM, I, Hofman A et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation* 2005; **111:** 570-75.

26. Allison MA, Denenberg JO, Nelson JJ, Natarajan L, Criqui MH. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. *J Vasc Surg* 2007; **46:** 500-06.

27. Corsetti JP, Rainwater DL, Moss AJ, Zareba W, Sparks CE. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in postinfarction patients. *Clin Chem* 2006; **52:** 1331-38.

28. Wassertheil-Smoller S, Kooperberg C, McGinn AP et al. Lipoprotein-associated phospholipase A2, hormone use, and the risk of ischemic stroke in postmenopausal women. *Hypertension* 2008; **51:** 1115-22.

29. Blake GJ, Dada N, Fox JC, Manson JE, Ridker PM. A prospective evaluation of lipoprotein-associated phospholipase A(2) levels and the risk of future cardiovascular events in women. *J Am Coll Cardiol* 2001; **38:** 1302-06.

30. Packard CJ, O'Reilly DS, Caslake MJ et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 2000; **343:** 1148-55.

31. Robins SJ, Collins D, Nelson JJ, Bloomfield HE, Asztalos BF. Cardiovascular events with increased lipoprotein-associated phospholipase A(2) and low high-density lipoprotein-cholesterol: the Veterans Affairs HDL Intervention Trial. *Arterioscler Thromb Vasc Biol* 2008; **28:** 1172-78.

32. Jackson LA. Description and status of the azithromycin and coronary events study (ACES). *J Infect Dis* 2000; **181:** S579-81.

33. The Lp-PLA_2 Studies Collaboration. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA_2 and cardiovascular diseases. *Eur J Cardiovasc Prev Rehabil* 2007; **14:** 3-11.

34. Cox DR. Regression Models and Life-Tables. *JRSSB* 1972; **34:** 187-220.

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177-88.

36. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980; 5-338.

37. Prentice R. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika* 1986; **73:** 1-11.

38. Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. *J Clin Epidemiol* 1999; **52:** 1165-72.

39. White IR. Multivariate random-effects meta-analysis. *Stata Journal* 2009; **9:** 40-56.

40. Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. *Stat Med* 1998; **17:** 2537-50.

41. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; **10:** 1025-35.

42. Plummer M. Improved estimates of floating absolute risk. *Stat Med* 2004; **23:** 93-104.

43. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903-13.

44. The Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005; **294:** 1799-809.

45. Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *J Clin Epidemiol* 2002; **55:** 86-94.

46. Thompson SG, Higgins JP. Can meta-analysis help target interventions at individuals most likely to benefit? *Lancet* 2005; **365:** 341-46.

47. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; **18:** 2693-708.

48. Collett D. *Modelling survival data in medical research*. London: Chapman & Hall; 1994.

49. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **10:** 101-29.

50. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557-60.

51. The Fibrinogen Studies Collaboration. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. *Am J Epidemiol* 2007; **166:** 867-79.

52. Clarke R, Shipley M, Lewington S et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; **150:** 341-53.

53. MacMahon S, Peto R, Cutler J et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990; **335:** 765-74.

54. The Fibrinogen Studies Collaboration. Regression dilution methods for meta-analysis: assessing long-term variability in plasma fibrinogen among 27 247 adults in 15 prospective studies. *Int J Epidemiol* 2006; **35:** 1570-78.

55. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med* 1989; **8:** 1051-69.

56. Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499-502