Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases

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Review

Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA$_2$ and cardiovascular diseases

The Lp-PLA$_2$ Studies Collaboration*

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Background **A large number of observational epidemiological studies have reported generally positive associations between circulating mass and activity levels of lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) and the risk of cardiovascular diseases. Few studies have been large enough to provide reliable estimates in different circumstances, such as in different subgroups (e.g., by age group, sex, or smoking status) or at different Lp-PLA$_2$ levels. Moreover, most published studies have related disease risk only to baseline values of Lp-PLA$_2$ markers (which can lead to substantial underestimation of any risk relationships because of within-person variability over time) and have used different approaches to adjustment for possible confounding factors.**

Objectives **By combination of data from individual participants from all relevant observational studies in a systematic 'meta-analysis', with correction for regression dilution (using available data on serial measurements of Lp-PLA$_2$), the Lp-PLA$_2$ Studies Collaboration will aim to characterize more precisely than has previously been possible the strength and shape of the age and sex-specific associations of plasma Lp-PLA$_2$ with coronary heart disease (and, where data are sufficient, with other vascular diseases, such as ischaemic stroke). It will also help to determine to what extent such associations are independent of possible confounding factors and to explore potential sources of heterogeneity among studies, such as those related to assay methods and study design. It is anticipated that the present collaboration will serve as a framework to investigate related questions on Lp-PLA$_2$ and cardiovascular outcomes.**

Methods **A central database is being established containing data on circulating Lp-PLA$_2$ values, sex and other potential confounding factors, age at baseline Lp-PLA$_2$ measurement, age at event or at last follow-up, major vascular morbidity and cause-specific mortality. Information about any repeat measurements of Lp-PLA$_2$ and potential confounding factors has been sought to allow adjustment for possible confounding and correction for regression dilution. The analyses will involve age-specific regression models. Synthesis of the available observational studies of Lp-PLA$_2$ will yield information on a total of about 15 000 cardiovascular disease endpoints.** ***Eur J Cardiovasc Prev Rehabil*** **14:3–11 © 2007 The European Society of Cardiology**

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Introduction

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is an enzyme that circulates largely bound to low-density lipoprotein [1]. Because it can hydrolyze oxidized phospholipids (which leads to the generation of pro-inflammatory products including lysophosphatidylcholine and oxidized free fatty acids), there is interest in the pro-inflammatory properties of Lp-PLA$_2$ [1,2]. This enzyme can, however, also hydrolyze platelet-activating factor (a factor which helps to activate platelets, monocytes, and macrophages), consistent with anti-inflammatory activity [3]. Available observational studies of the risk of cardiovascular diseases and various circulating markers

*The authors/steering group members, authors/operations group members, and authors/coordinating centre members of the Lp-PLA$_2$ Studies Collaboration are listed in the appendix to this article.
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Table 1 Prospective studies of lipoprotein-associated phospholipase A_2 and cardiovascular diseases published by May 2006

Study	Population/ sampling frame	Location	Year of baseline survey	Number of cases	Number of non-cases	Age range (years)	Male (%)	Assay		Endpoint assessed	Risk comparison	Risk ratio (95% CI)	
								Type	Source			Minimally adjusted[a]	Further adjusted[b]
ARIC [4,5]	Household lists/ random	USA	1987–1989	CHD: 608 Stroke: 194[d]	740	45–64	41	ELISA	DiaDexus PLAC test	CHD death, non-fatal MI, CRV, stroke	Top third vs. bottom third	CHD: 1.78 (1.33–2.38) Stroke: 2.23 (1.48, 3.34)[d]	CHD: 1.15 (0.81, 1.63) Stroke: 1.93 (1.14, 3.27)[d]
Mayo [6][c]	Angiography patients/ complete	USA	1998–1999	61	405	26–76	62	ELISA	DiaDexus PLAC test	CHD death, non-fatal MI, CRV, stroke	Per 1 SD increase	1.28 (1.06, 1.54)*	1.30 (1.06, 1.59)
MONICA/ KORA [7]	Population register/random	Germany	1984–1985	97	837	45–64	100	ELISA	DiaDexus PLAC test	CHD death, non-fatal MI	Per 1 SD increase	1.37 (1.16, 1.62)*	1.23 (1.02, 1.47)
OPUS – TIMI 22 [8][c]	ACS patients/ complete	Multinational	1997–1998	421	1930	21–96	73	Radiometric activity assay	In house	Death, non-fatal MI UR, RH, stroke	Top fifth vs. bottom fifth	0.64 (0.45, 0.90)*	0.96 (0.68, 1.36)
PROVE IT – TIMI 16 [8][c]	ACS patients/ complete	Multinational	2000–2001	995	2653	>18	78	Radiometric activity assay	In house	Death, non-fatal MI UA, CRV, stroke	Top fifth vs. bottom fifth	Baseline: 1.01 (0.85, 1.20)* 30 day: 1.50 (1.22, 1.85)*	Baseline: 1.08 (0.86, 1.36) 30 day: 1.33 (1.01, 1.74)
Rotterdam Study [9]	Household lists/ complete	Netherlands	1990–1993	CHD: 308 Stroke: 110[d]	1820	>55	38	Radiometric activity assay	In house	CHD death, non-fatal MI, stroke[d]	Top quarter vs. bottom fifth	CHD: 2.36 (1.58, 3.52) Stroke: 1.97 (1.04, 3.79)[d]	CHD: 1.97 (1.28, 3.02) Stroke: 1.97 (1.03, 3.79)
THROMBO [10][c]	MI patients/ complete	USA	1994–1998	122	644	23–92	77	Colorimetric activity assay	Cayman Chemical	CHD death, non-fatal MI, UA	Top quarter vs. bottom three quarters	1.86 (1.29, 2.68)	1.90 (1.31, 2.75)
WHS [11]	Female health professionals/ complete	USA	1992–1995	123	123	>45	0	ELISA	In house	CHD death, non-fatal MI, stroke	Top quarter vs. bottom quarter	1.73 (0.87, 3.44)	1.17 (0.45, 3.05)
WOSCOPS [12]	Coronary screening clinics/complete	UK	1989–1991	580	1160	45–64	100	ELISA	In house	CHD death, non-fatal MI, CRV	Per 1 SD increase	1.20 (1.08, 1.35)*	1.18 (1.05, 1.33)

ACS, acute coronary syndrome; ARIC, Atherosclerosis Risk In Communities study; CHD, coronary heart disease; CI, confidence interval; CRV, coronary revascularization; ELISA, enzyme-linked immunosorbent assay; MI, myocardial infarction; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; OPUS – TIMI 16, Orbofiban in Patients with Unstable Coronary Syndromes – Thrombolysis In Mycocardial Infarction 16; PROVE IT – TIMI 22, PRavastatin Or atorVastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22; RH, rehospitalisation; THROMBO, Thrombogenic Factors and Recurrent Coronary Events; UA, unstable angina; UR, urgent revascularization; WHS, Women's Health Study; WOSCOPS, West of Scotland Coronary Prevention Study. [a]The least adjusted estimate reported: either crude *or minimally adjusted (e.g. age and sex only). [b]Adjusted for a variety of known or suspected risk factors. [c]All study participants had pre-existing disease at baseline. [d]Ischaemic stroke.

Table 2 Collaborating prospective studies of lipoprotein-associated phospholipase A$_2$ and cardiovascular diseases known to be in progress but not reported by May 2006 (numbers of disease cases listed are only estimates)

Study	Population	Total number of participants[a]	Cases[a]	Disease
Cardiovascular Health Study	General	5800	1700	Various vascular outcomes
EPIC Norfolk	General	3600	1200	CHD
FRISC II	ACS	1400	200	Death, MI
GENICA	Prior CHD	1200	100	CVD
GUSTO IV	ACS	900	70	Mortality
Heart Protection Study	CV/DM	20000	4500	CVD
Intermountain	General	1500	230	CVD
Karola	Prior CHD	1000	100	CVD
Malmö	General	5000	250	CVD
NOMAS	Acute Stroke	500	100	CVD
Northwick Park II	General	3000	200	CHD
Nurses Health/Health Professionals	General	3000	1000	CVD
Nurses Health/Health Professionals	DM	2200	350	CVD
PROSPER	General	6000	900	CVD
Rancho Bernardo	General	2000	200	CHD
San Diego Vascular Cohort Study	Prior CVD	500	300	All cause mortality, CHD, CVD
VA-HIT	Prior CHD	1800	400	CVD
WHI-HBPSW	General	83000	930	Stroke

ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EPIC, European Prospective Investigation into Cancer; FRISC II, Fragmin and fast Revascularisation in Instabilitiy in Coronary artery disease trial; GENICA, Genetic and Environmental factors in Coronary Atherosclerosis; GUSTO IV, Global Utilitzation of Strategies to Open Occluded Arteries IV; Karola, Langzeiterfolge der KARdiologischen Anschlussheilbehandlung; NOMAS, Northern Manhattan Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; VA-HIT, Veterans Affairs HDL Intervention Trial; WHI – HBPSW, Women's Health Initiative (ancillary study: Hormones and Biomarkers Predicting Stroke in Women). [a]Approximate numbers (Lp-PLA$_2$ measurements in some studies will involve nested case-control or case-cohort susbsets, for example the WHI – HBPSW study has Lp-PLA$_2$ information for 930 cases and 1014 controls).

of Lp-PLA$_2$ (typically involving measurement of platelet activating factor actylehydrolase mass or activity) have reported generally positive associations (Table 1) [4–12]. These studies have, however, generally involved too few coronary heart disease (CHD) cases (and even fewer cases of other types of vascular disease) to enable a reliable assessment of associations under different circumstances (such as at different ages; in women and men; at different levels of other risk factors), or of the shape of any dose–response relationship. Moreover, most studies have related CHD risk to the baseline measurements of Lp-PLA$_2$ (which can lead to substantial underestimation of any association due to 'regression dilution' [13]) and have involved different approaches to adjustment for possible confounding factors [14].

Objectives of the Lp-PLA$_2$ Studies Collaboration

By appropriate combination of data from individual participants from all relevant observational studies in a systematic meta-analysis, with correction for regression dilution, the Lp-PLA$_2$ Studies Collaboration aims to characterize more reliably than has previously been possible the age and sex-specific relevance of Lp-PLA$_2$ to CHD. This protocol prospectively defines the main objectives, and study identification, data collection and statistical methods to be used.

The primary objectives of the collaboration are to assess the age and sex-specific associations of Lp-PLA$_2$ with CHD making appropriate allowances for regression dilution bias; to determine to what extent associations of Lp-PLA$_2$ and CHD are independent of possible confounding factors; and to enable detailed exploration of potential sources of heterogeneity among studies, involving study-level characteristics (such as assay methods, features of study design, geographical location) and personal characteristics (such as age, sex, and levels of several established risk factors). Secondary objectives include initiation of investigations of Lp-PLA$_2$ circulating markers with stroke and with other vascular conditions, and of Lp-PLA$_2$ genotypes with cardiovascular disease outcomes [15–24]. It is anticipated that the present collaboration will serve as a framework for evidence emerging from studies on Lp-PLA$_2$ and cardiovascular outcomes, not only for studies which are already published, but also for those known to be in progress and those yet to be identified (Tables 1 and 2).

Identification of relevant studies and collection of data

Selection criteria and identification of studies

Eligible prospective studies are those that have recorded baseline circulating Lp-PLA$_2$ measurements in participants and subsequent cardiovascular disease outcomes. Studies listed in Tables 1 and 2 were identified through computer-assisted literature searches of databases, scanning of reference lists, hand-searching of relevant journals, and correspondence with authors of relevant reports. The list of eligible studies will continue to be updated until at least 2007.

Baseline covariates and characteristics to be studied

Data have been sought from investigators on Lp-PLA_2 values recorded at the baseline survey and at any subsequent surveys during follow-up to allow for study-specific correction for regression dilution [13]. To investigate the relevance of possible confounding factors and effect modifiers, data have been sought (where available) from baseline on ethnicity; total cholesterol; high and low-density lipoprotein cholesterol; triglycerides; apolipoproteins A1 and B; systolic and diastolic blood pressure; acute phase reactants (e.g., C-reactive protein, fibrinogen, albumin, white cell count); haemostatic factors (e.g., von Willebrand factor, fibrin D-dimer); metabolic factors (eg, fasting glucose and insulin); history of coronary heart disease, stroke and diabetes; weight and height; waist and hip circumference; smoking; alcohol consumption; use of cardiovascular medications (including those allocated in randomized trials) and exogenous hormones; physical activity; and socio-economic status (Fig. 1). In addition, data from all subsequent examinations have been sought on Lp-PLA_2 values, serum lipids, blood pressure, and other recorded biochemical factors. Collection of data on age at baseline and at the disease event (or at last follow-up) and sex will enable age and sex-specific analyses. Collection of information on the different assay methods and standards used in Lp-PLA_2 measurement [25] and on features of study design (e.g., case–control versus prospective cohort studies) will enable exploration of any heterogeneity among study results. Categorical variables, such as alcohol consumption, physical activity and smoking, will be re-coded to maximize comparability among studies.

Outcomes to be studied

For each individual, data have been sought on any of the following outcomes and on their dates of occurrence: non-fatal myocardial infarction (MI); 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 cases have been sought from each study (as have data on the completeness of follow-up in the prospective studies). Analyses will be based on events classified according to the International Classification of Diseases (or, where this is not available, on available study-specific classification systems).

Data transfer and checking

Data can be transferred from the individual studies to the coordinating centre using any machine-readable medium and in any format convenient to the collaborators. Risk factor and outcome data will be accepted in whatever

Fig. 1

From baseline examination (i.e. the time point at which blood samples for Lp-PLA_2 measurements were collected)

- A unique (but anonymous) identifier
- Date of birth (or age at baseline) and sex
- A matching identifier for case–control pairs for studies in which controls are 'individually matched' to cases

Baseline survey (biochemistry, clinical measurements etc. made at the same time point as described above)

- Lp-PLA_2 values (both **mass** and **activity** levels, if available)
- Ethnicity
- Smoking and alcohol use (current / ex / never; amount / duration etc.)
- Use of cardiovascular medications (current and past use, in as much detail as possible, including anti-hypertensive drugs, 'statins', fibrates) – also, treatment allocation made in randomized controlled trials (RCTs)
- Use of postmenopausal hormone therapy or oral contraceptives
- Prior history of coronary heart disease [in particular myocardial infarction (MI) and angina], stroke, transient ischaemic attack and diabetes
- Systolic and diastolic blood pressure
- Weight, height, waist and hip circumference
- Physical activity and socio-economic status
- Total, high-and low-density lipoprotein cholesterol (including particle size and numbers, where available); triglycerides; lipoprotein (a); apolipoprotein-AI and -B (including information about fasting status at time blood samples were taken)
- 'Inflammatory' markers (including C-reactive protein, fibrinogen, albumin and white cell count)
- Creatinine, uric acid
- Haemostatic factors (including von-Willebrand factor, fibrin D-dimer)
- Metabolic factors (including fasting glucose and insulin)

From re-survey examinations

- The unique (but anonymous) identifier used for baseline visit
- Date of the visit (or, if not available, age at visit)
- Data on baseline items that were collected at repeat surveys (particularly Lp-PLA_2, serum lipids and other biochemical factors)

Non-fatal events during follow-up

- Myocardial infarction and date of MI
- Stroke (including subtype if available: e.g., ischaemic/haemorrhagic) and date of stroke
- Other subsidiary cardiovascular outcomes: e.g. angina, peripheral vascular disease (PVD), coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PCTA), congestive heart failure
- Dates of censoring for end of follow-up for non-fatal events

Fatal events during follow-up

- Date last known to be alive (if not recorded as dead)
- Date of death (or, if not available, age at death)
- Underlying cause of death (preferably coded according to some specified version of the three-digit International Classification of Diseases; but if a three-digit ICD code is not available then whatever code the study already uses)
- Date of censoring for end of follow-up for fatal cases

List of variables to be sought (where available) from relevant studies of circulating lipoprotein-associated phospholipase A_2 (Lp-PLA_2) levels.

format they were originally coded and stored by the study investigators. The data obtained from each participating study will be checked for consistency by the secretariat and any queries then referred back, in confidence, to the study collaborators. The data will then be converted to a standard format for incorporation into a central database to be used for collaborative analyses. The content of the data will be unchanged by this process, and computer-generated detailed summary tabulations based on the converted data will be returned to each collaborator for review and confirmation.

Confidentiality of data provided

The data provided from each study will remain entirely the property of the principal investigators of that study, and will be held in confidence by the coordinating centre. Anonymous data on individual participants in each of the studies will be stored securely on the computer database at the coordinating centre.

Statistical analyses

Principal analyses

The main analyses will involve regression models stratified by study and sex (and, in randomized trials, by treatment allocation). Studies provided as prospective cohort studies will be analysed using Cox's proportional hazards model [26]. The principal outcome will be a combination of CHD death or first MI, with subsidiary investigation of other vascular outcomes such as stroke, congestive heart failure and recurrent non-fatal MI (consideration of such specific associations should enable an assessment of the overall impact of Lp-PLA$_2$ on cardiovascular disease). Separate assessments will be made of associations between Lp-PLA$_2$ markers and relevant outcomes in individuals with and without evidence of baseline cardiovascular disease (with attempts, where possible, to stratify analyses by extent and type of baseline cardiovascular disease: for example, those with stable CHD versus unstable CHD at the time of blood collection). Apparent heterogeneity between the results of different studies will be explored partly by fitting formal interaction terms in the regression models, and partly by grouping studies by various characteristics (such as by assay method, by sample size or by study design features) and then comparing the subtotals. The effect of adjustment for established risk factors (such as smoking and serum lipid concentrations) and other characteristics will be investigated. Analyses will be presented separately by sex and by age group (where the data are sufficient to sustain such subdivisions), and any effect modification by age, sex, duration of follow-up and established risk factors (in particular, low-density lipoprotein cholesterol concentrations) will be investigated by formal tests of interaction. Exploratory analyses will be conducted that restrict attention to cases who had outcomes several years after the baseline survey (for prospective cohort studies) and to participants without evidence of vascular disease at baseline (both of which should minimize any influence of pre-existing disease). As different studies have used different Lp-PLA$_2$ assay methods (based on either mass or activity levels) and different assay technologies (with later studies using subsequent 'generations' of kits), this collaboration provides an opportunity to determine to what extent data from studies with such different characteristics can be pooled; previous collaborative meta-analyses have involved similar considerations [26].

Regression models will be used in two ways to describe any dose–response relationships. The first will involve the estimation of regression coefficients per unit increase in exposure (i.e., the risk ratio per nanomole per minute per millilitre in 'usual' plasma Lp-PLA$_2$ activity or per nanogram per millilitre in 'usual' Lp-PLA$_2$ mass levels). But such estimates will merely describe the steepness of the straight lines that best fit the data when risk is plotted on a logarithmic scale. A fuller description of the shape of the relationships will be obtained by plotting the risk ratios in groups defined by increasing baseline levels of Lp-PLA$_2$ against the mean 'usual' levels of Lp-PLA$_2$ (see below) [27]. Confidence intervals for each risk factor level will be estimated using 'floating' variances, which do not alter the estimates of the risk ratios but reduce the variance attributed to those that are not exactly unity (and should also greatly reduce the unwanted covariances between them) [28].

Adjustment for regression dilution

Analyses will be adjusted for the effects of regression dilution bias using previously described methods [13]. For analyses describing the steepness of the straight-line association between risk on a logarithmic scale and Lp-PLA$_2$ values, an adjustment factor can be estimated from the relationship between baseline and follow-up Lp-PLA$_2$ levels. For analyses describing the shape of the risk relationship, the adjustment will be performed by plotting risk ratios for groups subdivided by increasing baseline Lp-PLA$_2$ values against the means of the repeat measurements made during follow-up in those groups. These provide an unbiased estimate of the 'usual' Lp-PLA$_2$ during follow-up. Wherever possible, re-measurements from within each contributing study will be used, but where these data are not available correction factors will be estimated from available data in comparable studies. Previous reports have shown that, although the magnitude of the regression dilution bias for cholesterol and blood pressure did not depend strongly on age, sex or ethnicity, it did depend strongly on the duration of follow-up [13]. This will be investigated for Lp-PLA$_2$ and, if appropriate, adjustments for regression dilution will depend on the average interval between Lp-PLA$_2$ measurement and the event of interest. If possible, similar estimates will be used to adjust for within-person fluctuations of possible confounding factors.

Table 3 **Selected published studies of polymorphisms in the lipoprotein-associated phospholipase A_2 gene (*PLA2G7*) and cardiovascular diseases**[a]

Author	Location	Outcome	Number of individuals genotyped		Genotype (cases)[b]			Genotype (controls)[b]			Case population	Control population	Male (%)[c]	Mean age (years)[c]
			Cases	Controls	1/1	1/2	2/2	1/1	1/2	2/2				
							ALA379VAL							
Abuzeid 2003 [15]	Multinational	MI	527	566	320	183	24	340	186	40	MI patients	General population	100/100	52/52
Campo 2004 [16]	Sicily	Carotid IMT	76	114	12	29	35	16	44	54	Lipid clinic referrals	Lipid clinic referrals	57/49	57/57
Ninio 2004 [17]	Germany	Coronary stenosis	1298	484	847	396	55	270	193	21	Angiography patients	Volunteers or routine GP check-up	75/73	62/60
							ARG92HIS							
Campo 2004 [16]	Sicily	Carotid IMT	76	114	36	36	4	54	52	8	Lipid clinic referrals	Lipid clinic referrals	57/49	57/57
Ninio 2004 [17]	Germany	Coronary stenosis	1303	484	691	517	95	289	173	22	Angiography patients	Volunteers or routine GP check-up	75/73	62/60
							ILE198THR							
Campo 2004 [16]	Sicily	Carotid IMT	76	114	8	30	38	12	46	56	Lipid clinic referrals	Lipid clinic referrals	57/49	57/57
							VAL279PHE							
Ichihara 1998 [18]	Japan	DCM	122	226	74	44	4	173	49	4	Hospitalized patients	Routine hospital check-up	71/76	56/54
Ito 2002 [19]	Japan	Coronary spasm	214	212	155	53	6	153	52	7	Hospitalized patients	Angiography referrals	49/49	61/61
Unno 2000 [20]	Japan	Coronary stenosis	104	114	66	34	4	87	25	2	Hospitalized patients	Gastrointestinal screening patients	86/NS	71/70
Yamada 2000 [21]	Japan	83% MI, 17% stroke	850	1684	512	310	28	1176	459	49	Hospitalized patients, NS	Routine hospital check-up	71/55	62/47
Yamada 2002 [22]	Japan	MI	445	464	NS	NS	NS	NS	NS	NS	Hospitalized patients	Individuals with RF but no history of CAD	49/50	57/58
Yoshida 1998 [23]	Japan	Brain haemorrhage	99	270	57	36	6	191	74	5	Consecutive patients	Routine hospital check-up	56/56	62/60
Zhang 2005 [24]	China	Cerebral infarction	102	215	66	33	3	171	40	4	NS	Healthy individuals, NS	NS	NS

CAD, coronary artery disease; DCM, dilated cardiomyopathy; GP, general practitioner; IMT, intima–media thickness; MI, mycocardial infarction; NS, not specified; RF, at least one established risk factor. [a]The lipoprotein-associated phospholipase A_2 gene is sometimes referred to as the platelet activating factor acetylhydrolase (PAF-AH) gene. [b]Genotype frequencies are presented for common homozygotes (1/1), heterozygotes (1/2) and rare homozygotes (2/2) respectively. [c]Data presented separately for cases/controls.

Genetic studies

Literature-based meta-analyses of genetic association studies (such as those listed in Table 3) [15–24], supplemented by tabular data from investigators, will be conducted to help quantify associations more reliably between relevant Lp-PLA$_2$ gene variants, circulating Lp-PLA$_2$ levels and disease risk. The results of such analyses will help to determine if pooling of individual data on these genetic factors will be prioritized in the present collaboration.

Study management and co-ordination

A steering group, comprising principal investigators of studies contributing individual data to the collaboration (with regular updates of the group's membership to encompass emerging studies), will meet at least once a year. Steering group members will provide input to an operations group (described below) and have opportunities to comment on draft analyses and texts prior to submission of manuscripts for publication, and will be authors of any reports including their data. Investigators will retain the right to withdraw their data from some or all of the meta-analyses at all times. An operations group – comprising representatives of the contributing principal investigators, coordinating centre, study funders, and other agreed members – will meet face-to-face about twice a year, with regular interim teleconferences. This group will provide oversight for the collaboration, particularly by establishing research priorities, setting and monitoring project milestones, and supervising the work of publications committees. An independent academic coordinating centre (jointly based in the Department of Public Health and Primary Care, University of Cambridge, and the Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford) will be responsible for the collection, harmonization, maintenance and pooling of datasets provided by principal investigators, and for helping to lead analyses and interpretation of results. The coordinating centre will provide regular reports to the steering group and to the operations group. Only the coordinating centre will have direct access to the combined dataset.

Publication policy

This protocol has been circulated to collaborating investigators prior to submission for publication for comments and agreement, and, as described above, this procedure will be followed for all other manuscripts from this collaboration. As with this report, all subsequent reports from the collaboration will be published in the name of the Lp-PLA$_2$ Studies Collaboration. The initial submission for publication of the main results is scheduled for 2007 and will be confined to analyses concerning the stated objectives. The timing of subsequent publications will be discussed with collaborating investigators to allow them time to publish their own analyses before any collaborative report emerges.

Conclusion

The Lp-PLA$_2$ Studies Collaboration is a consortium of investigators of prospective studies of Lp-PLA$_2$ and cardiovascular disease. By combining individual participant data from such studies, the proposed meta-analysis should help to determine more reliably than previously possible the strength of any independent association, the shape of any dose–response relationship with risk, the magnitude of associations in different circumstances (such as age-specific and sex-specific associations), and sources of heterogeneity between studies. Furthermore, data from repeated measurements of Lp-PLA$_2$ and related factors taken some years apart will allow appropriate correction for regression dilution, leading to associations of disease risk with long-term 'usual' Lp-PLA$_2$ levels after appropriate adjustment for potential confounding factors. The collaboration will include data from several studies involving a total of approximately 15 000 patients with major cardiovascular disease outcomes.

Appendix

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