

Impact of Aspirin on Primary Prevention of Cardiovascular Events in Patients with Elevated Lipoprotein(a): A Systematic Review and Meta-analysis

Daniel Caldeira^{1,2,3,4}, Mariana Alves^{4,5}, Rita Avó-Baião⁴, Andreia Lopes⁴, Luisa Prada⁶, Fausto J Pinto^{1,2}

1. Centro Cardiovascular da Universidade de Lisboa - CCUL, CAML, Faculdade de Medicina, Universidade de Lisboa, Portugal.
2. Serviço de Cardiologia, ULS de Santa Maria, Portugal.
3. Centro de Estudos de Medicina Baseado na Evidência (CEMBE), Faculdade de Medicina, Universidade de Lisboa, Portugal.
4. Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Portugal.
5. Serviço de Medicina, ULS Santa Maria, Lisboa, Portugal.
6. Clinical Research Unit, Research Center of IPO Porto CI-IPOP@RISE (Health Research Network), Portuguese Oncology Institute of Porto (IPO Porto)/Porto Comprehensive Cancer Center (Porto.CCC), Porto, Portugal.

Corresponding author

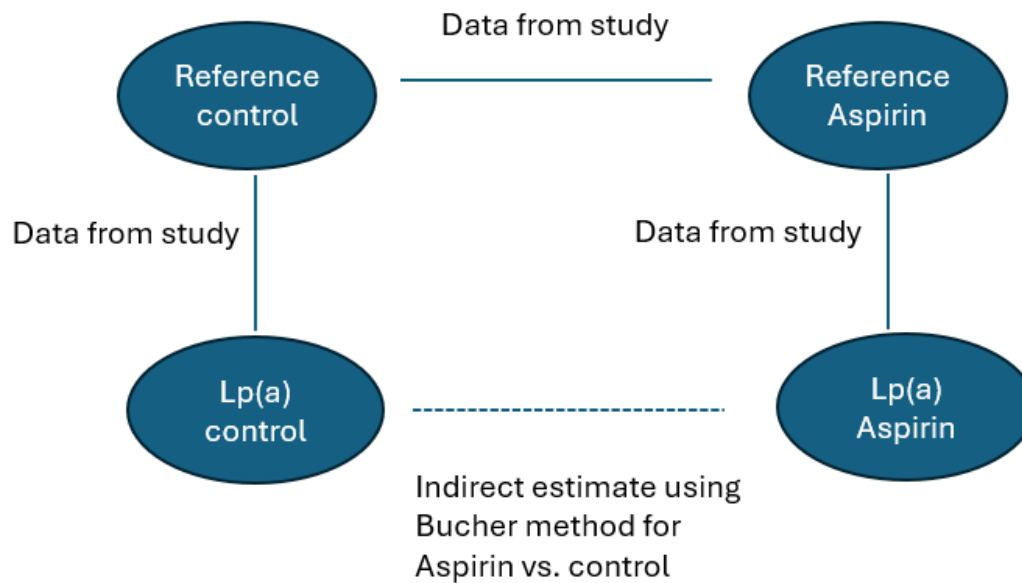
Prof. Daniel Caldeira

Centro Cardiovascular da Universidade de Lisboa - CCUL, Faculdade de Medicina, Universidade de Lisboa, Portugal. Av. Prof. Egas Moniz, Lisboa 1649-028, Portugal;
dgcaldeira@hotmail.com

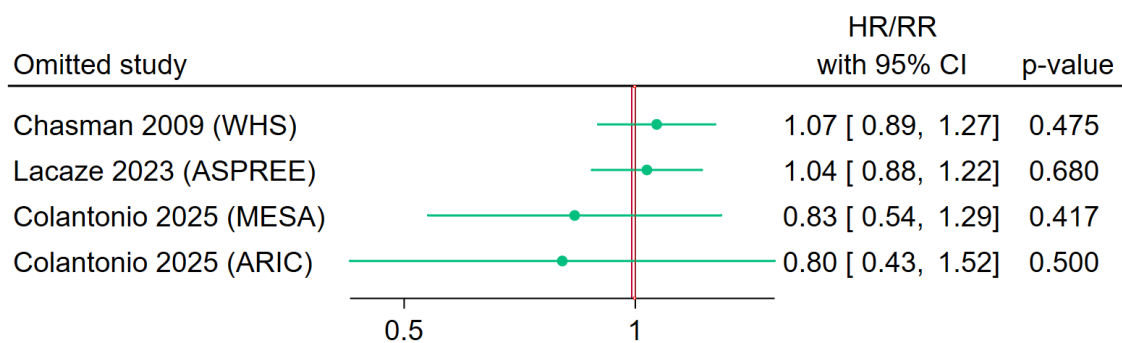
Supplementary Table 1: Search strings

Search Strategy:

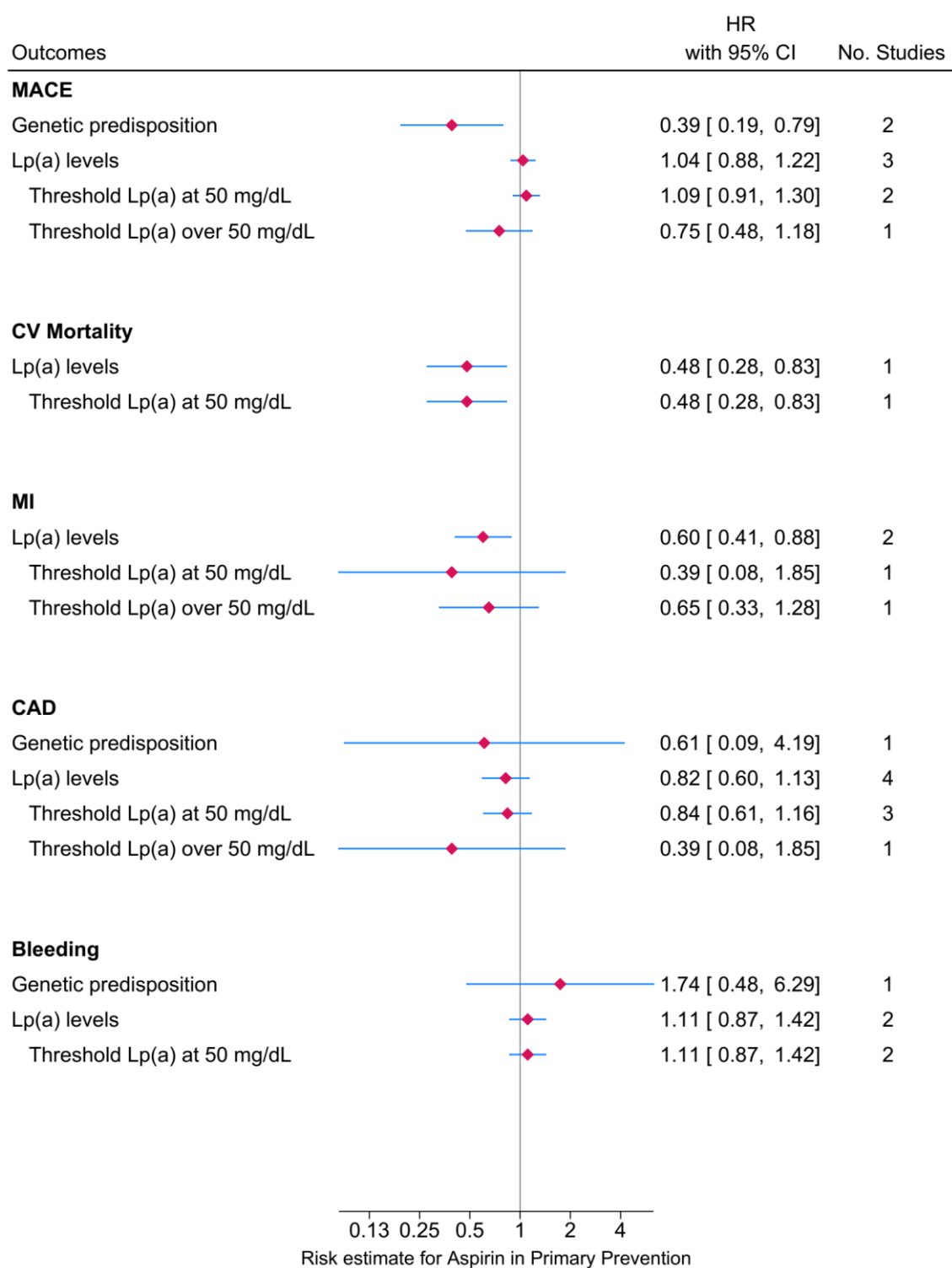
#	Searches	Results
	MEDLINE AND CENTRAL via OVID	156 records
1	exp aspirin/	
2	aspirin.af.	
3	exp Platelet Aggregation Inhibitors/	
4	acetylsalicylic acid.af.	
5	1 or 2 or 3 or 4	
6	exp "lipoprotein(a)"/	
7	"lipoprotein(a)".af.	
8	"lipoprotein(a)".af.	
9	"lp(a)".af.	
10	6 or 7 or 8 or 9	
11	5 and 10	
	Web of Science Core Collection	116 records
1	aspirin (All Fields)	
2	ALL=("lipoprotein(a)")	
3	ALL=("lp(a)")	
4	#1 AND (#2 OR #3)	



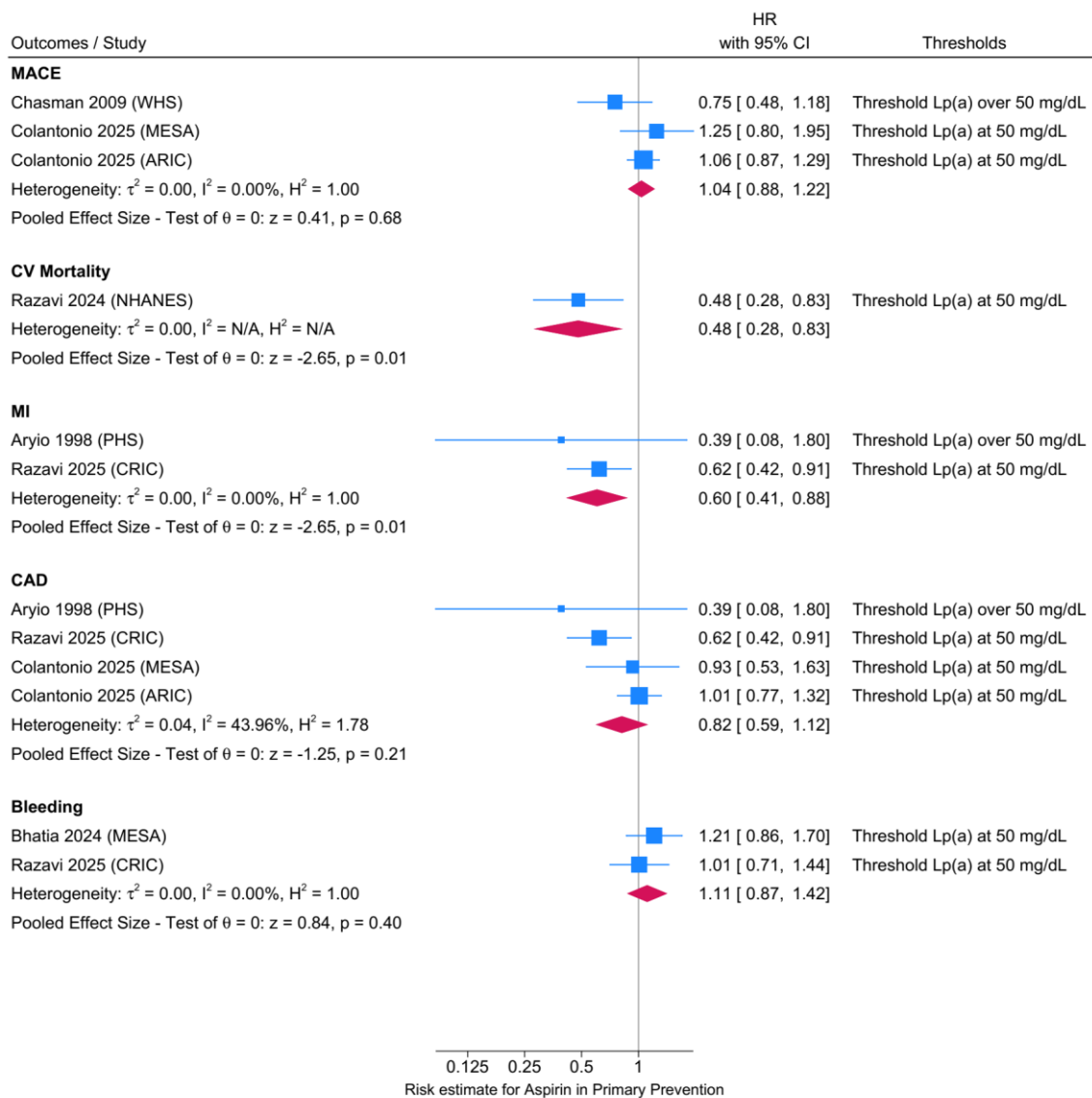
Supplementary Figure 1: Method used to retrieve the MI estimate in PHS study.



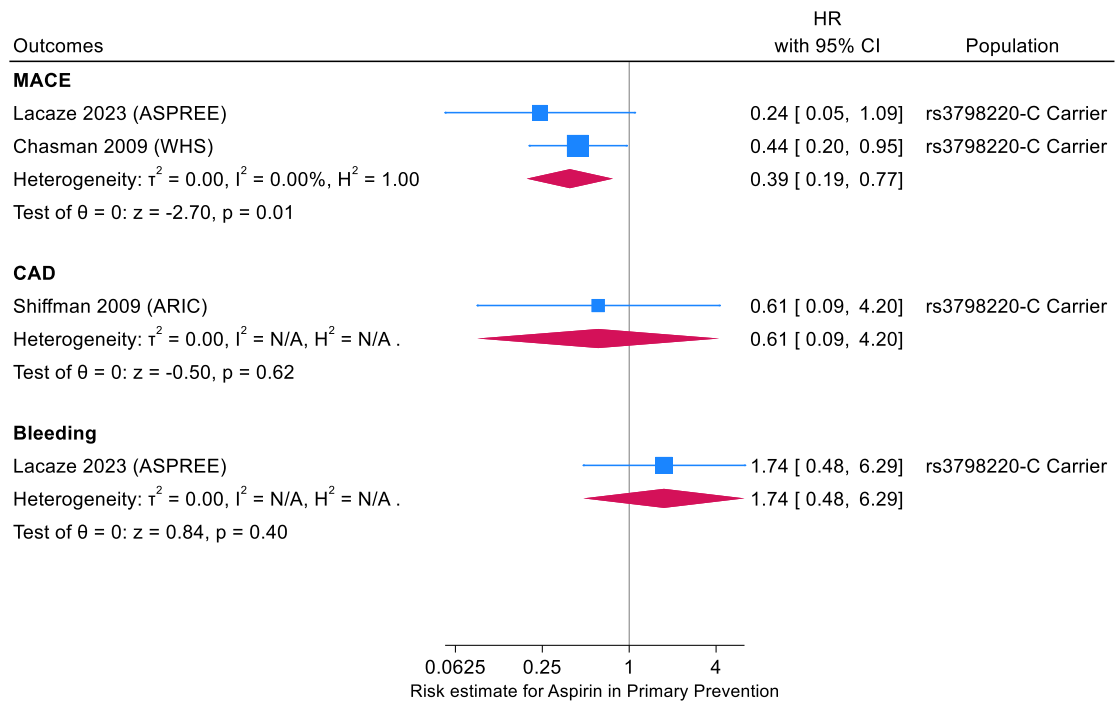
Supplementary Figure 2: Jackknife leave-one-out meta-analysis for the primary outcome (Red line refers to the central estimate of the main analysis; Black line is the null effect line).



Supplementary Figure 3: Forest plot with the results of the analysis according to the criteria for inclusion (i.e. according to the Lp(a) levels or genetic predisposition) and Lp(a) thresholds used by studies.



Supplementary Figure 4: Forest plot with the results of the analysis with the detailed data using the Lp(a) levels as inclusion criterion.



Supplementary Figure 5: Forest plot with the results of the analysis with the detailed data using the genetic predisposition for increased Lp(a) as inclusion criterion.

Supplementary Table 1: Results of individual studies a pooled analysis, with the weights of each study in the analyses.

Study	Year	Population	MACE events
Lacaze <i>et al.</i> ¹⁸ <i>ASPREE</i> <i>subgroup</i>	2022	rs3798220-C Carrier: 406 High LPA-GRS: 2556	rs3798220-C Carrier: 18 (4.4%) High LPA-GRS: 105 (4.1%)
Ariyo <i>et al.</i> ¹⁹ <i>PHS</i>	1998	95 th Percentile: ~ 30*	No MACE event rate reported
Chasman <i>et al.</i> ¹⁷ <i>WHS</i> <i>subgroup</i>	2009	417	19 (4.5%)
Razavi <i>et al.</i> ¹⁵ NHANES III	2024	612	No MACE event rate reported
Colantonio <i>et al.</i> ¹⁶ <i>ARIC</i>	2025	1204	421 (34.9%)
Colantonio <i>et al.</i> ¹⁶ <i>MESA</i>	2025	506	80 (15.8%)
Razavi <i>et al.</i> ¹⁴ CRIC	2025	687	No MACE event rate reported

*Assuming from 95th percentile from a Assuming a right skewed sample from Ariyo et al (1998) data.

Bucher methods:

Estimate risk calculations

$$\log(\text{HR A vs B}) = \log(\text{HR A vs C}) - \log(\text{HR B vs C})$$

Standard error calculation

$$\text{SE}^2_{\text{indirect (A vs B)}} = (\text{SE}^2 \text{ A vs C}) + (\text{SE}^2 \text{ B vs C})$$

Confidence intervals calculations

$$\exp(\log(\text{HR}) \pm 1.96 \times \text{SE})$$

Supplementary Table 2: Results of individual studies in the pooled analysis, with the weights of the contribution of each study in the analyses.

Study	HR	[95% CI]		Weight (%)
Outcome: MACE				
Bhatia 2024 (MESA)	0.54	0.315	0.926	20.3
Chasman 2009 (WHS)	0.75	0.478	1.176	2.2
Colantonio 2025 (MESA)	1.25	0.803	1.947	20.8
Colantonio 2025 (ARIC)	1.06	0.874	1.286	56.7
Pooled Effect Size	0.989	0.788	1.243	
Outcome: CV Mortality				
Razavi 2024 (NHANES)	0.48	0.279	0.826	100.0
Outcome: MI				
Aryio 1998 (PHS)	0.39	0.088	1.734	6.29
Razavi 2025 (CRIC)	0.62	0.421	0.913	93.71
Pooled Effect Size	0.602	0.414	0.876	
Outcome: CAD				
Aryio 1998 (PHS)	0.39	0.088	1.734	4.26
Razavi 2025 (CRIC)	0.62	0.421	0.913	32.06
Colantonio 2025 (MESA)	0.93	0.53	1.631	21.07
Colantonio 2025 (ARIC)	1.01	0.774	1.317	42.61
Pooled Effect Size	0.815	0.592	1.122	
Outcome: Bleeding				
Bhatia 2024 (MESA)	1.21	0.863	1.696	46.8
Lacaze 2023 (ASPREE)	1.74	0.481	6.294	8.3
Razavi 2025 (CRIC)	1.01	0.707	1.443	45.0
Pooled Effect Size	1.129	0.887	1.436	