

Abstract

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Genetically elevated lipoprotein(a) and increased risk of myocardial infarction.

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CONTEXT: High levels of lipoprotein(a) are associated with increased risk of myocardial infarction (MI).

OBJECTIVE: To assess whether genetic data are consistent with this association being causal.

DESIGN, SETTING, AND PARTICIPANTS: Three studies of white individuals from Copenhagen, Denmark, were used: the Copenhagen City Heart Study (CCHS), a prospective general population study with 16 years of follow-up (1991-2007, n = 8637, 599 MI events); the Copenhagen General Population Study (CGPS), a cross-sectional general population study (2003-2006, n = 29 388, 994 MI events); and the Copenhagen Ischemic Heart Disease Study (CIHDS), a case-control study (1991-2004, n = 2461, 1231 MI events).

MAIN OUTCOME MEASURES: Plasma lipoprotein(a) levels, lipoprotein(a) kringle IV type 2 (KIV-2) size polymorphism genotype, and MIs recorded from 1976 through July 2007 for all participants.

RESULTS: In the CCHS, multivariable-adjusted hazard ratios (HRs) for MI for elevated lipoprotein(a) levels were 1.2 (95% confidence interval [CI], 0.9-1.6; events/10,000 person-years, 59) for levels between the 22nd and 66th percentile, 1.6 (95% CI, 1.1-2.2; events/10,000 person-years, 75) for the 67th to 89th percentile, 1.9 (95% CI, 1.2-3.0; events/10,000 person-years, 84) for the 90th to 95th percentile, and 2.6 (95% CI, 1.6-4.1; events/10,000 person-years, 108) for levels greater than the 95th percentile, respectively, vs levels less than the 22nd percentile (events/10,000 person-years, 55) (trend $P < .001$). Numbers of KIV-2 repeats (sum of repeats on both alleles) ranged from 6 to 99 and on analysis of variance explained 21% and 27% of all variation in plasma lipoprotein(a) levels in the CCHS and CGPS, respectively. Mean lipoprotein(a) levels were 56, 31, 20, and 15 mg/dL for the first, second, third, and fourth quartiles of KIV-2 repeats in the CCHS, respectively (trend $P < .001$); corresponding values in the CGPS were 60, 34, 22, and 19 mg/dL (trend $P < .001$). In the CCHS, multivariable-adjusted HRs for MI were 1.5 (95% CI, 1.2-1.9; events/10,000 person-years, 75), 1.3 (95% CI, 1.0-1.6; events/10,000 person-years, 66), and 1.1 (95% CI, 0.9-1.4; events/10,000 person-years, 57) for individuals in the first, second, and third quartiles, respectively, as compared with individuals in the fourth quartile of KIV-2 repeats (events/10,000 person-years, 51) (trend $P < .001$). Corresponding odds ratios were 1.3 (95% CI, 1.1-1.5), 1.1 (95% CI, 0.9-1.3), and 0.9 (95% CI, 0.8-1.1) in the CGPS (trend $P = .005$), and 1.4 (95% CI, 1.1-1.7), 1.2 (95% CI, 1.0-1.6), and 1.3 (95% CI, 1.0-1.6) in the CIHDS (trend $P = .01$). Genetically elevated lipoprotein(a) was associated with an HR of 1.22 (95% CI, 1.09-1.37) per doubling of lipoprotein(a) level on instrumental variable analysis, while the corresponding value for plasma lipoprotein(a) levels on Cox regression was 1.08 (95% CI, 1.03-1.12).

CONCLUSION: These data are consistent with a causal association between elevated lipoprotein(a) levels and increased risk of MI.

