

# Genetically elevated levels of lipoprotein associated with increased risk of heart attack

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A genetic analysis of data from three studies suggests that genetically elevated levels of lipoprotein(a) are associated with an increased risk of heart attack, according to a study in the June 10 issue of *JAMA*.

Myocardial infarction (MI; heart attack) remains a leading cause of illness and death despite targeting of low-density lipoprotein (LDL) cholesterol by statin therapy. "The need for identification of additional causal factors, and thus potential new targets for prophylactic treatment, is apparent. Elevated levels of lipoprotein(a) [a LDL particle bound to a plasminogen-like glycoprotein, apolipoprotein(a)] represent such a candidate; however, whether lipoprotein(a) causes MI is unclear. A randomized intervention trial showing that a reduction in lipoprotein(a) levels leads to a reduction in risk of MI would favor causality. Such a study has yet to be conducted," the authors write. They add that a mendelian (genetics) randomization study could also provide evidence of a causal relationship. "Simply put, association of elevated levels of lipoprotein(a), as well as association of [genetic variation](#) raising levels of lipoprotein(a), with risk of MI would suggest causality."

Levels of lipoprotein(a) may vary up to a thousand-fold among individuals, and levels are partly determined by variations in the LPA gene coding for the apolipoprotein(a) moiety (any equal part) of lipoprotein(a). The most influential LPA variation is the kringle IV type 2 (KIV-2) size variation. The number of KIV-2 repeats correlates inversely with levels of lipoprotein(a), according to background information in the article.

Pia R. Kamstrup, M.D., of Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark, and colleagues examined whether genetically elevated lipoprotein(a) levels are associated with increased risk of MI. Three studies of white individuals from Copenhagen, Denmark, were used: the Copenhagen City Heart Study (CCHS), a general population study with 16 years of follow-up (1991-2007, n = 8,637, 599 MI events); the Copenhagen General Population Study (CGPS), a 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 = 2,461, 1,231 MI events). For all participants, plasma lipoprotein(a) levels, lipoprotein(a) KIV-2 size variation genotype, and MIs were recorded from 1976 through July 2007.

The researchers found: "We observed an increase in risk of MI with increasing levels of lipoprotein(a), as well as with decreasing numbers of lipoprotein(a) KIV-2 repeats associated with elevated levels of lipoprotein(a). The increase in risk of MI associated with genetically elevated levels of lipoprotein(a) was consistently seen in 3 large independent studies...", they write. "The KIV-2 genotype explained 21 percent and 27 percent of the total lipoprotein(a) concentration variation in the CCHS and the CGPS. Instrumental variable analysis (in which the increase in lipoprotein[a] levels explained by the KIV-2 genotype was related to MI) directly demonstrated that genetically elevated lipoprotein(a) is associated with increased risk of MI, like elevations in plasma lipoprotein(a). These findings are consistent with a causal association of elevated lipoprotein(a) levels with increased MI risk."

"Nonetheless, final proof of causality still requires randomized clinical trials demonstrating reduced MI risk in response to [lipoprotein \(a\)](#)-lowering therapy."

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