Circulation

RESEARCH LETTER

Lipoprotein(a) in Alzheimer, Atherosclerotic, Cerebrovascular, Thrombotic, and Valvular Disease

Mendelian Randomization Investigation

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Lipoprotein(a) (Lp[a]) is a circulating lipoprotein with proatherogenic, proinflammatory, and possibly prothrombotic properties. Circulating Lp(a) levels are largely genetically determined, in particular, by the *LPA* gene. As such, genetic variants at the *LPA* locus can serve as instrumental variables for investigating the clinical effects of circulating Lp(a) levels. Mendelian randomization (MR) studies have shown that elevated Lp(a) levels are associated with a higher risk of coronary artery disease[1–3] and aortic valve stenosis.[2–4] Evidence on the causal role of elevated Lp(a) levels for other atherosclerotic and specific valvular diseases is limited, although there are MR data supporting a positive association between genetically predicted Lp(a) levels and peripheral artery disease.[2,3] Whether Lp(a) is causally related to thrombotic disease and cerebrovascular disease remains unclear.[2,3,5]

In this study, we used the UK Biobank cohort to perform an MR investigation into the causal effects of circulating Lp(a) levels on atherosclerotic, cerebrovascular, thrombotic, and valvular diseases. Because a recent MR study provided evidence of an inverse association of Lp(a) levels with Alzheimer disease,[5] we additionally explored whether genetically predicted Lp(a) levels are associated with Alzheimer disease and dementia.

This study included 367 586 unrelated European-descent UK Biobank participants. Outcomes were defined based on *International Classification of Diseases and Related Health Problems* codes, and self-reported data validated by interview with a nurse. Incident cases were recorded until March 31, 2017, and deaths were recorded until February 14, 2018. The UK Biobank was approved by the North West Multicentre Research Ethics Committee, and all participants provided written informed consent.

We used a genetic instrument comprising 43 single-nucleotide polymorphisms (at the *LPA* locus) conditionally associated with Lp(a) levels at genome-wide significance in 27 540 European-descent participants from the CHD Exome+ Consortium (no overlap with UK Biobank).[1] Genetic associations with Lp(a) were taken from the CHD Exome+ Consortium and were additionally validated in UK Biobank. The instrument explained 61.0% of the variance in Lp(a) levels in UK Biobank. Effect sizes of the single-nucleotide polymorphisms–outcome associations were estimated in UK Biobank using logistic regression under an additive model with adjustment for age, sex, and 10 principal components of ancestry. MR estimates were obtained using the inverse variance–weighted method with adjustment for correlations among the single-nucleotide polymorphisms.

The associations with the outcomes per genetically predicted 50-mg/dL increase in Lp(a) levels are shown in the Figure. Our results support a strong causal relationship between Lp(a) levels and coronary artery disease. The observed odds ratio was 1.36 (95% CI, 1.32–1.40), which is similar to the previously observed association in the CHD Exome+ Consortium (odds ratio rescaled per 50-mg/dL

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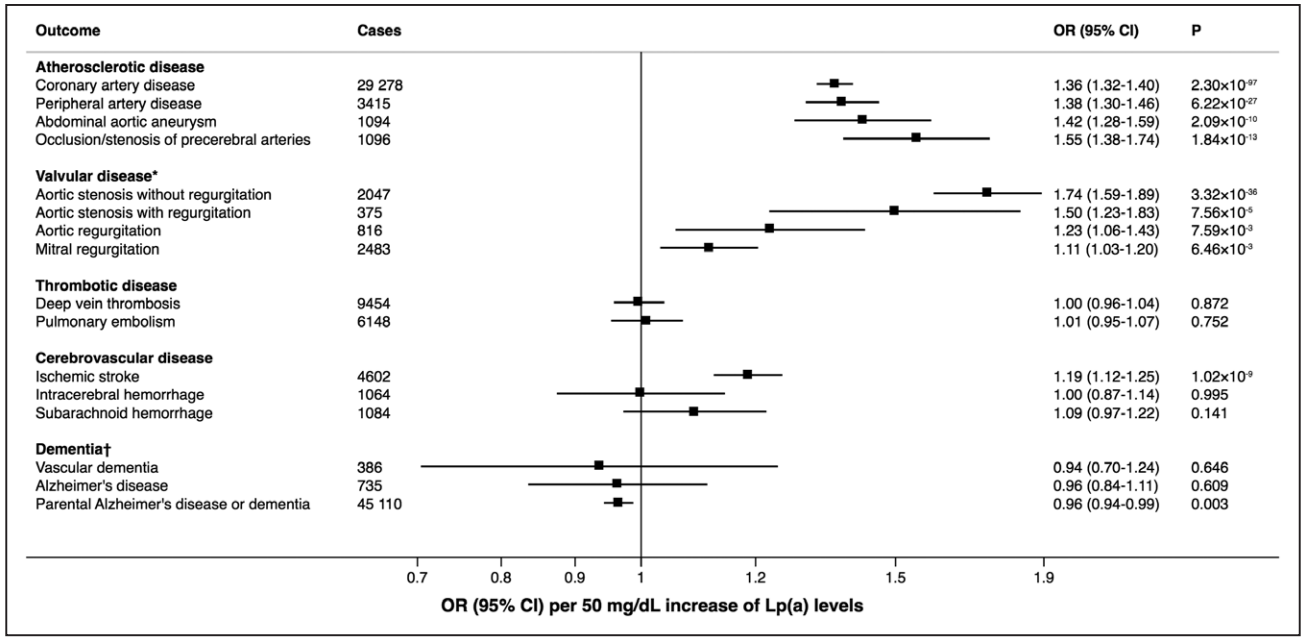

Figure. Associations of genetically predicted Lp(a) levels with atherosclerotic, valvular, thrombotic, and cerebrovascular diseases and dementia. *Excluding rheumatic valvular disorders. †Vascular dementia and Alzheimer disease are defined based on an individual's routinely collected medical outcomes, whereas parental Alzheimer disease or dementia is defined as self-report of a family history of Alzheimer disease or dementia. Genetic associations with parental Alzheimer disease or dementia are less likely to suffer from selection bias or survivor bias, because participation in UK Biobank is less likely to be influenced by the medical history of an individual's parents. Lp(a) indicates lipoprotein(a); and OR, odds ratio.

increment of Lp[a] levels, 1.35 [95% CI, 1.29–1.41]).[1] We observed even stronger associations between genetically predicted Lp(a) levels and peripheral artery disease, abdominal aortic aneurysm, occlusion or stenosis of precerebral arteries, and aortic stenosis with or without regurgitation. Novel findings were positive associations of genetically predicted Lp(a) levels with both aortic and mitral regurgitation. Our findings support a previously reported modest association between genetically predicted Lp(a) levels and ischemic stroke,[2,5] and a null association with venous thromboembolism as well.[2,3] We found null associations with hemorrhagic stroke subtypes. Although we found null associations with Alzheimer disease and vascular dementia, possibly attributable to lack of power, our study revealed a weak inverse association of genetically predicted Lp(a) levels with self-reported parental history of Alzheimer disease or dementia. All results were consistent when using a genetic instrument comprising the 2 single-nucleotide polymorphisms (rs10455872 and rs3798220) used in several previous MR studies.[3–5]

The mechanism behind the associations of Lp(a) levels with aortic regurgitation without concomitant aortic stenosis and mitral regurgitation is unclear, but it could possibly be related to degenerative change from calcific aortic valve disease known to be associated with Lp(a) levels. Aortic valve sclerosis represents a significant proportion of the underlying pathogenesis of isolated aortic regurgitation. Likewise, mitral annular calcification may interfere with mitral valve closure and increase mitral regurgitation, which represented >90% of all mitral valve disease cases. Last, aortic stenosis may also create or worsen mitral regurgitation.

An advantage of our study is that we assess and compare the associations of genetically predicted Lp(a) levels with atherosclerotic, cerebrovascular, thrombotic, and valvular diseases in a single population of individuals of European descent. This, however, limited the generalizability of our results to other populations. Another limitation is that outcomes were defined in part by validated self-reported disease, which could lead to some misclassification of outcome.

In conclusion, this MR study supported Lp(a) as a causal risk factor for atherosclerotic and valvular diseases but not for thrombotic disease and hemorrhagic stroke subtypes. These findings may be used to inform the design of further research toward the treatment and prevention of atherosclerotic and valvular diseases. Whether lowered Lp(a) levels increase the risk of dementia needs further investigation.

ARTICLE INFORMATION

Data sharing: The data that support the findings of this study are available from the corresponding author on reasonable request. The UK Biobank data are available on application (http://www.ukbiobank.ac.uk/register-apply).

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