Raising 'good' cholesterol fails to protect against heart disease

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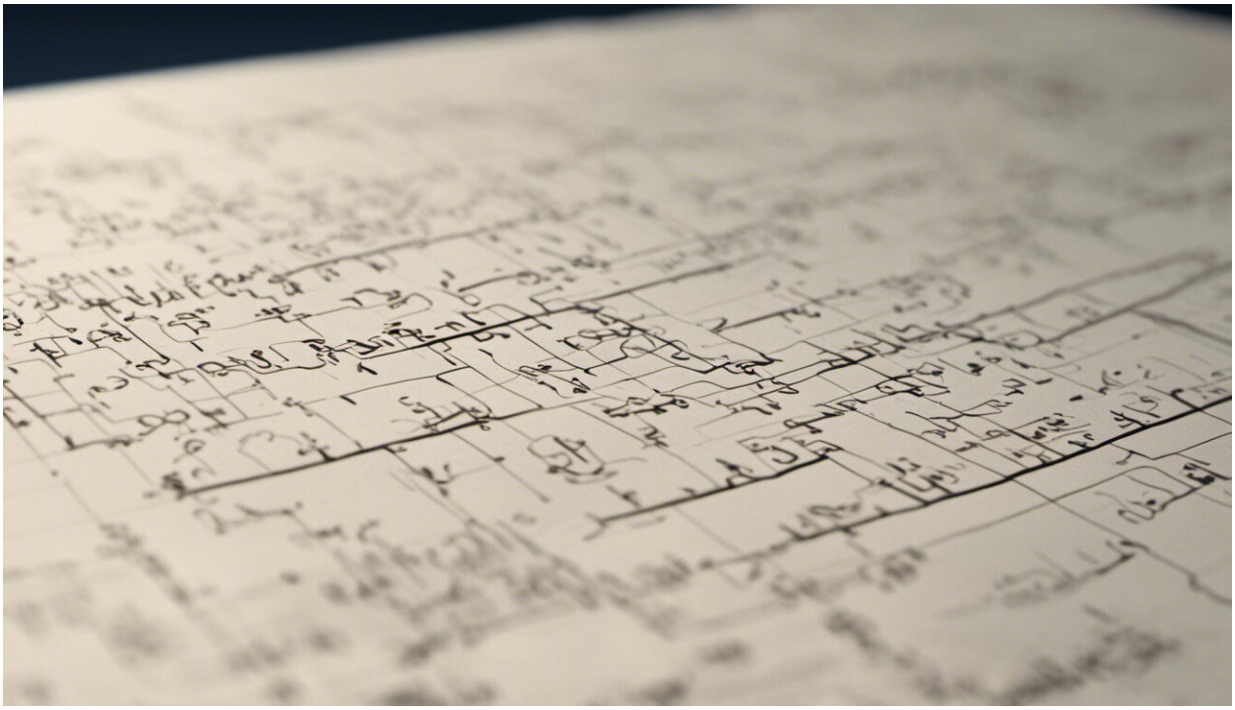

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Raising so-called 'good' cholesterol by blocking a key protein involved in its metabolism does not protect against heart disease or stroke, according to a large genetic study of 150,000 Chinese adults published in the journal *JAMA Cardiology*.

There are two types of cholesterol in the blood: LDL-C, so-called 'bad' cholesterol, which is carried in low-density lipoproteins (LDL), and HDL-C, so-called 'good' cholesterol which is found in high-density lipoproteins (HDL).

Lowering LDL-C (e.g. by statins) has been demonstrated to reduce the risk of heart diseases and stroke, but the causal role of HDL-C is less clear even though observational studies have shown an inverse association between HDL-C and risk of cardiovascular diseases.

Cholesterol ester transfer protein (CETP) transfers cholesterol between different lipoproteins. Blocking this protein, which raises levels of HDL-C as well as causing other changes to blood lipids, is a potentially important approach for prevention and treatment of cardiovascular diseases. Genetic variants which alter the activity of CETP can mimic some of the effects of drugs which target this protein and can be used to help assess the potential benefits and harms of this cholesterol-modifying treatment.

Researchers at the University of Oxford, Peking University and Chinese Academy of Medical Sciences explored the health effects of CETP genetic variants, including an East Asian specific functional variant, in 150,000 Chinese adults enrolled into the China Kadoorie Biobank (CKB). After ten years of follow-up, over 5,000 study participants had coronary heart disease and 19,000 had a stroke.

The researchers found that CETP genetic variants raised levels of HDL-C substantially, but did not lower LDL-C and did not lower the risk of cardiovascular diseases such as heart disease and stroke. There was also no effect on atherosclerotic plaques and thickness of the arteries, or on other conditions such as diabetes and kidney disease. However, the study found increased risk of eye diseases as a possible adverse effect of CETP inhibition, a finding which is supported by other genetic studies in

East Asian and Western populations.

In this study of genetic variants which alter CETP activity, raising HDL-C without also lowering LDL-C did not result in a benefit for heart disease or stroke. The study results complement findings from the recent REVEAL clinical trial of the CETP inhibitor anacetrapib, which found that beneficial effects of CETP inhibition for heart disease were more likely to be due to lowering 'bad' cholesterol LDL-C than raising 'good' HDL-C.2.

New treatments are discovered by exploring biological pathways that cause disease but can be modified by drugs. The journey from basic biology to large-scale randomised trials in humans is long and expensive: the estimated cost of getting a single product to market is over $2 billion. Using genetic data to predict the benefits and harms of new treatments can reduce costs and improve the drug development pipeline.

This approach is likely to become much more widely used to examine the causal nature of biological pathways involved in diseases before mounting large-scale clinical trials in the future. Many thousands of functional genetic variants are known which may represent potential drug targets in different biological pathways, and the research teams are using the same approach to assess a number of other important therapeutic targets.

Study author Dr Iona Millwood, from the University of Oxford, said: "Our research has helped clarify the role of different types of cholesterol , and suggests that raising levels of HDL-C by blocking CETP activity, without also lowering LDL-C, does not confer any major benefits for cardiovascular disease."

Professor Liming Li, study co-author from Peking University, said: "CKB is a powerful resource for collaborative research that can inform

not only the relevance of lifestyle factors (e.g. smoking, diet and physical activity) for health but also drug development."

Professor Zhengming Chen, study co-author at the University of Oxford, added: "This study demonstrates the value of large prospective biobank studies with genetic data linked to health records, carried out in diverse global populations, to predict the potential benefits or harms of new drug treatments."

The full paper, "Association of CETP Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults," is published in the journal *JAMA Cardiology*.

More information: Iona Y. Millwood et al. Association of CETP Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults, *JAMA Cardiology* (2017). DOI: 10.1001/jamacardio.2017.4177

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