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'Good' cholesterol mutation linked to heart disease

Genetic study deals blow to the idea that high levels of HDL cholesterol reduce heart risk.

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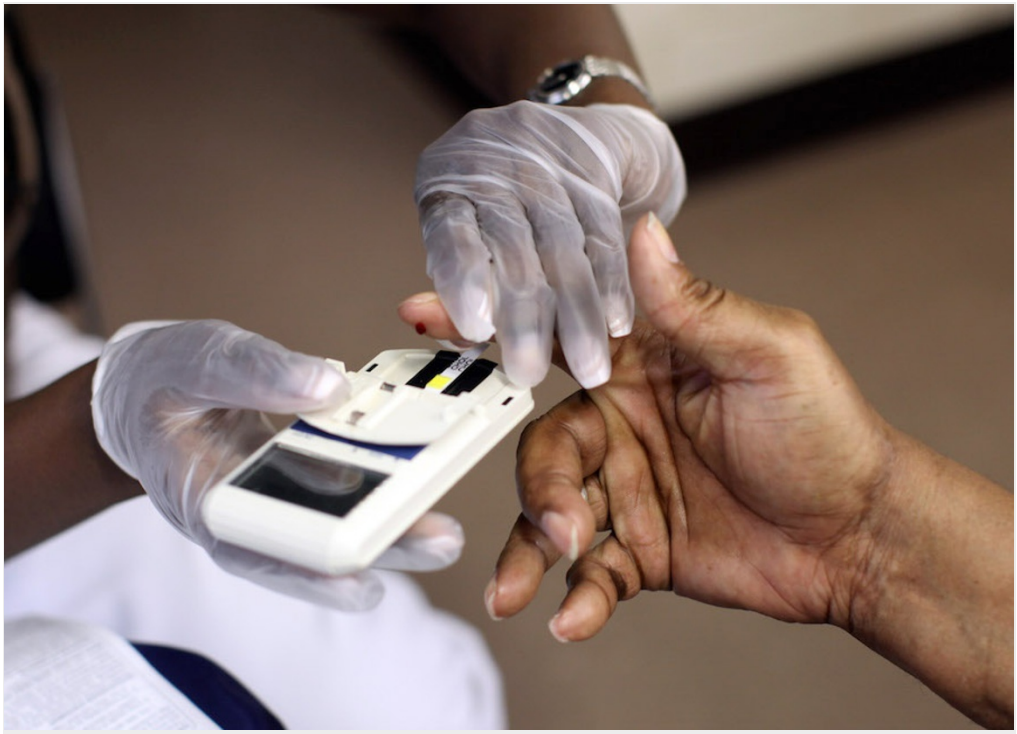

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Many heart drugs seek to lower levels of 'bad' LDL cholesterol.

For decades, guidance on cholesterol levels has come as a tidy dichotomy: LDL cholesterol is ‘bad’ for heart health; HDL cholesterol is ‘good’. But a genetic study adds to mounting evidence that the truth is not so simple — and that having high levels of HDL cholesterol may not protect against heart disease.

The study, published on 10 March in *Science*[1], pitted the genomes of 852 people with high levels of HDL (high-density lipoprotein) cholesterol in their blood against those of a control group of 1,156 people with low HDL cholesterol.

The approach unearthed mutations in a protein called SR-BI that binds to HDL cholesterol and triggers its movement from the blood into the liver. Those who carried the mutations tended to have high HDL cholesterol levels in the blood, as expected. But they were also, paradoxically, at higher risk for coronary heart disease.

“When I started medical school in 1992, I was taught that anything that raised HDL cholesterol must be good for you,” says Sekar Kathiresan, a preventative cardiologist at the Massachusetts General Hospital in Boston, and a co-author of the study. “We can now safely disregard that notion.”

Cause versus effect

LDL cholesterol is believed to collect in the walls of blood vessels, ultimately blocking the flow of blood and leading to heart attacks and strokes. A large body of genetic and molecular studies, and the rampant success of some drugs that lower LDL cholesterol, back up this idea.

The role of HDL, however, has been less clear. Although higher HDL cholesterol levels are correlated with better heart health, efforts to show that HDL cholesterol has a protective effect in humans have come up empty-handed.

Pharmaceutical companies have poured millions of dollars into the pursuit of drugs that would raise HDL cholesterol. So far, none has

been shown to protect the heart. One promising compound, called anacetrapib and developed by Merck of Kenilworth, New Jersey, is in late-stage clinical trials. But the drug also lowers LDL cholesterol, making it difficult to infer whether its effects on heart health are truly related to HDL cholesterol, cautions Monty Krieger, a molecular cell biologist at the Massachusetts Institute of Technology in Cambridge.

Krieger's team has shown that mice that lacked SR-BI had high levels of HDL cholesterol in their blood[2]. But despite HDL cholesterol's 'good' reputation, the mice also had high rates of plaque build-up in their arteries, a condition known as atherosclerosis.

It was important to find out whether the same would be true in humans, notes Krieger, because of key differences in mouse and human physiology. Mice, for example, tend to have less LDL than humans.

Kathiresan and his colleagues found 19 people with at least one copy of the mutation in SR-BI. Sixteen of those participants also had high HDL cholesterol levels. One woman was the first person found to have two copies of the mutation.

A cleaner study

That represents a breakthrough, says Jay Heinecke, an endocrinologist at the University of Washington in Seattle. Previous genetic analyses in humans were confounded by a focus on genes that could affect physiology in other ways, for example by altering the levels of other fatty molecules called triglycerides. "This is a cleaner study," he says. "This will force us to re-evaluate how we've been thinking about HDL cholesterol from the beginning."

But Krieger, who agrees that the study is important, notes that SR-BI could have other functions that have not yet been characterized, and that many animal studies have suggested a role for HDL cholesterol in protecting against heart disease.

Kathiresan's study also raises an important question: why are higher levels of HDL cholesterol in the blood associated with reduced heart risk? Some have argued that other functions of HDL cholesterol — not fully reflected by its concentration in the blood — could be important. Kathiresan suspects that people with high HDL cholesterol levels may also be better at clearing triglycerides from the blood.

For now, Kathiresan thinks there is evidence that physicians should change how they discuss HDL-cholesterol with their patients. "We probably should stop using the term good cholesterol," he says.

Explaining the difference between correlation and causation makes for a more complicated conversation, he adds. "The analogy I use is grey hair: if you have grey hair, you are at higher risk of heart disease on average," Kathiresan says. "But that's not because of the grey hair."

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References

1. Zanoni, P. *et al*. *Science* **351**, 1166–1171 (2016).
2. Trigatti, B. *et al*. *Proc. Natl Acad. Sci. USA* **96**, 9322–9327 (1999).