

'Bad' cholesterol not the only culprit linked with a higher likelihood of heart disease

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"Bad" cholesterol isn't the only culprit linked with a higher risk of cardiovascular disease, according to a trio of recent University of Alberta studies—including landmark global research—showing that a

different kind of cholesterol is also a strong risk factor for people worldwide.

Remnant [cholesterol](#) (RC) was confirmed as a strong risk factor for [coronary heart disease](#), heart attacks and stroke, the [largest of the studies](#) showed. RC is produced from the metabolism of triglycerides that come from sources of dietary fat and from the body's own stores of cholesterol particles.

Using [genomic data](#) from a combined sample of almost one million participants—spanning Africa, Asia, North America and Europe—the findings, published in *Arteriosclerosis, Thrombosis, and Vascular Biology*, are the first to show, on such a large scale, a causal link between high RC and risk of cardiovascular illness.

"This tells us that the health risk posed by high RC is of greater concern than the traditional LDL cholesterol which is our current goal of prevention and therapy," says Paolo Raggi, senior author of the study and professor of cardiology in the Faculty of Medicine & Dentistry.

The researchers found that having elevated RC led to a 1.5 times higher risk for coronary heart disease, a 1.6 times higher risk of [heart attack](#) and a 1.2 times higher risk of stroke.

A fuller picture of cardiovascular risk

Two studies drawing on Alberta data are also the first to confirm the relationship—and highlight the risk—of heart disease and high RC for the Canadian population.

High RC levels were linked with greater risk of developing heart disease, according to one of the [studies](#), published in *CMAJ Open*, involving 14,000 middle-aged and older Albertans.

Additionally, the levels of RC were high regardless of whether people were already on medication for, or had normal or low levels of low-density lipoprotein cholesterol (LDL-C), commonly known as "bad" cholesterol, the research showed.

"We've provided new evidence that RC may be key in understanding the complete picture of cardiovascular risk and why people continue to have poor heart health despite achieving appropriate levels of LDL," says Spencer Proctor, a professor in the Division of Human Nutrition within the Faculty of Agricultural, Life & Environmental Sciences and one of the senior authors on the work.

"For the first time, we are showing that one of those risk factors could be RC."

Because [medical screening](#) for RC is less common than for LDL-C in Canada, it means the additional risk to people already susceptible to future heart attacks could be missed, says Proctor, who co-led the research team on the pair of Alberta studies, in collaboration with Dean Eurich, a professor in the U of A's School of Public Health.

"If LDL cholesterol is the only type measured and the level is found to be quite low—perhaps because it is being controlled by medication—that may seem like the risk of a cardiovascular event is lower. But that is an incomplete diagnostic picture, which should include assessment for RC."

Proctor, Eurich and their teams drew on data from the Alberta's Tomorrow Project, a long-term study that began tracking the health of 55,000 adults in the province in 2000, investigating why some people develop cancer and chronic diseases like heart disease and diabetes.

In analyzing the information, they found that people with heart disease

had 15% higher levels of RC in their blood, but not LDL-C levels, which were much lower, at 7%.

The results also showed that for every increase of one unit of RC in the blood, there was a 150% higher risk of having an event such as a heart attack, versus a 73% higher risk for LDL-C.

"LDL-C, in this case, isn't useful to predict future risk because people are possibly on medication," says Proctor.

Similar findings for people with diabetes

A [related study](#) published in *Diabetic Medicine* exploring the same questions about the benefits of RC assessment for people with diabetes showed similar results.

The researchers found that compared to those without the disease, people with diabetes had 22% higher levels of RC, almost 5% greater incidence of cardiovascular disease and 50% more probability of having other risk factors such as obesity. They were also 30% more likely to be on cholesterol-lowering medication, and consequently had 23% lower levels of LDL-C.

The findings are crucial given that diabetes already heightens the risk of cardiovascular disease, Proctor notes.

"We know that having diabetes is equivalent to having existing heart disease, and the risk remains elevated even after reducing LDL-C with medication. We don't have a good way—other than monitoring that [bad cholesterol](#)—of understanding how much risk there is for people with diabetes, so using RC measurements may be even more important for monitoring heart health."

Recognizing an overlooked indicator

Collectively, the studies confirm RC as a factor that can't be overlooked when assessing patients at risk of cardiovascular disease, says Proctor.

"The findings highlight the need to consistently include RC alongside LDL-C measurements. By taking the RC measurement, it can increase the accuracy of predicting whether someone will have a heart attack. If we can detect that early, doctors can provide the right medication, lifestyle and diet changes."

The findings should prompt a revision of current Canadian and worldwide guidelines for [medical professionals](#) to include RC as a lipid parameter that should be routinely measured, Raggi notes.

"The [medical community](#) worldwide needs to recognize remnant cholesterol as a significant player in influencing the cardiovascular health of the population."

Guideline changes would also "give doctors and specialists more information about patients taking medication to lower their LDL cholesterol, who might still be at risk of having a heart attack," Proctor adds.

The research could also help determine whether and how existing medications used for LDL-C can potentially lower RC, leading to the development of new drugs, he notes.

"We need to continue exploring what can help complete the diagnostic picture for everyone—with or without diabetes—at risk of [heart disease](#)."

More information: Eliano P. Navarese et al, Independent Causal

Effect of Remnant Cholesterol on Atherosclerotic Cardiovascular Outcomes: A Mendelian Randomization Study, *Arteriosclerosis, Thrombosis, and Vascular Biology* (2023). DOI: [10.1161/ATVBAHA.123.319297](https://doi.org/10.1161/ATVBAHA.123.319297)

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