

# Both Low and High HDL-C Levels Predict Infections in Population-Based Cohort

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COPENHAGEN, DENMARK — High and low levels of HDL cholesterol predicted increased risk of infectious disease, especially gastroenteritis and bacterial pneumonia, in a large population-based cohort study<sup>[1]</sup>.

The finding says nothing about cause and effect but is consistent with other studies suggesting that HDL plays a role in immunity, say researchers, who propose that it might help explain infection risks observed in some clinical trials of HDL-modifying therapies.

Of 97,166 persons followed in the longitudinal [Copenhagen General Population Study](#), 9% experienced an infectious-disease hospitalization over a median of 6 years, according to the report published December 8, 2017 in the *European Heart Journal*, with lead author Dr Christian M Madsen (Copenhagen University Hospital, Herlev, Denmark).

The risk across baseline levels of HDL cholesterol appeared U-shaped. The hazard ratio (HR) for those with baseline HDL-C <0.08 mmol/L (31 mg/dL) was 1.75 (95% CI 1.31–2.34), the report notes. For those with HDL-C >2.6 mmol/L (100 mg/dL), it was 1.43 (1.16–1.76). Both HRs were compared with people with HDL-C in the midrange of 2.2–2.3 mmol/L (85–95 mg/dL).

A similar pattern was observed for levels of apolipoprotein A1. No significant relationship was seen between infection risk and triglyceride levels.

When a confirmation analysis was conducted on another population-based cohort, 9387 patients from the [Copenhagen City Heart Study](#), the lower HDL-C concentration was associated with an HR of 2.00 (1.16–3.43) for any infectious-disease hospitalization, and the higher concentration was associated with an HR of 1.13 (0.80–1.60), both compared with the midrange HDL-C concentration.

That points to increased infectious-disease risk for low HDL but not for high HDL; that is, the risk in the confirmation cohort didn't follow a U-shaped curve.

Senior author Dr Børge G Nordestgaard (Copenhagen University Hospital) told *theheart.org | Medscape Cardiology* that in both cohorts, there were far more people in the low HDL range than in the high range. Therefore, he said, in the overall much smaller confirmation cohort there were probably too few people at high HDL levels for the increased risk to be apparent.

"Overall, the present study provides novel evidence on the link between HDL and infection-related outcomes. Although the authors cannot definitely prove a causal relationship between low and high HDL-C and infections, it is highly likely that HDL may indeed modulate the outcome of and the susceptibility for infectious diseases," write Drs Thimoteus Speer and Stephen Zewinger (Saarland University Medical Center, Homburg/Saar, Germany) in an accompanying editorial<sup>[2]</sup>.

"Nevertheless, despite the large study size and the sensitivity analyses provided, the presence of additional confounders or reverse causation cannot be fully excluded."

According to Nordestgaard, the findings are consistent with his group's earlier study<sup>[3]</sup> in which high levels of HDL-C predicted an increased risk of death from any cause.

A [meta-analysis of population-based studies](#) in Canada reached much the same conclusion.

Acknowledging it as speculation, Nordestgaard wondered whether it could have been simply chance that several trials of drugs that raise HDL-C also saw signals of increased infection risk [without showing a clinical benefit](#). Those included trials of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib, such as [ILLUMINATE](#), and of niacin, such as [HPS2-THRIVE](#).

A subgroup analysis in the current study saw that the adjusted HR for gastroenteritis was 1.66 (95% CI 1.08–2.55) and for bacterial pneumonia was 1.35 (95% CI 1.03–1.76) for persons with HDL-C under 1.0 mmol/L (39 mg/dL) compared with those with HDL-C >2.0 mmol/L (77 mg/dL).

By the same token, HRs for bacterial pneumonia, skin infection, and urinary-tract infection were significantly increased among those with HDL-C at the higher concentrations.

Both low and high HDL-C levels were associated with risk of likely bacterial infection, but only low HDL-C levels were predictive of risk of viral infections, according to the report.

"It is likely that the explanation for high infectious-disease risk differ in individuals with low and high HDL cholesterol," according to the authors. Both they and the editorialists describe potential mechanisms at length, much of it speculation.

HDL appears to be involved in promoting immunity in a number of ways, including serving as a removal vehicle for bacterial endotoxins, Nordestgaard said. But an infection risk with high HDL, he said, may well be due to HDL species that are dysfunctional.

"I think the scientific world has been misled by studying HDL [in ways] that were irrelevant," Nordestgaard said. That low levels of HDL-C promote cardiovascular disease while high levels protect against it is a "misguided hypothesis," he said.

"The reason low HDL is associated with more cardiovascular disease is probably just confounding, because when you have low HDL, you have high triglycerides," he said. "But what we're studying here now is not explained by triglycerides."

*Neither Madsen, Nordestgaard, nor the other authors had relevant financial relationships, nor did the editorialists.*

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## References

1. Madsen CM, Varbo A, Tybjaerg-Hansen A, Frikke-Schmidt R, Nordestgaard BG. U-shaped relationship of HDL and risk of infectious disease: two prospective population-based cohort studies. *Eur Heart J* 2017; DOI:10.1093/eurheartj/ehx665. [Article](#)
2. Speer T, Zewinger S. High-density lipoprotein (HDL) and infections: A versatile culprit. *Eur Heart J* 2017; DOI:10.1093/eurheartj/ehx734. [Editorial](#)
3. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: Two prospective cohort studies. *Eur Heart J* 2017; 38:2478–2486. [Article](#)

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