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Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis.

[Pedersen SB](#)¹, [Langsted A](#)¹, [Nordestgaard BG](#)².

Author information

Abstract

IMPORTANCE: Severe hypertriglyceridemia is associated with increased risk of acute pancreatitis. However, the threshold above which triglycerides are associated with acute pancreatitis is unclear.

OBJECTIVE: To test the hypothesis that nonfasting mild-to-moderate hypertriglyceridemia (177-885 mg/dL; 2-10 mmol/L) is also associated with acute pancreatitis.

DESIGN, SETTING, AND PARTICIPANTS: This prospective cohort study examines individuals from the Copenhagen General Population Study in 2003 to 2015 and the Copenhagen City Heart Study initiated in 1976 to 1978 with follow-up examinations in 1981 to 1983, 1991 to 1994, and in 2001 to 2003. Median follow-up was 6.7 years (interquartile range, 4.0-9.4 years); and includes 116 550 individuals with a triglyceride measurement from the Copenhagen General Population Study (n = 98 649) and the Copenhagen City Heart Study (n = 17 901). All individuals were followed until the occurrence of an event, death, emigration, or end of follow-up (November 2014), whichever came first.

EXPOSURES: Plasma levels of nonfasting triglycerides.

MAIN OUTCOMES AND MEASURES: Hazard ratios (HRs) for acute pancreatitis (n = 434) and myocardial infarction (n = 3942).

RESULTS: Overall, 116 550 individuals were included in this study (median [interquartile range] age, 57 [47-66] years). Compared with individuals with plasma triglyceride levels less than 89 mg/dL (<1 mmol/L), the multivariable adjusted HRs for acute pancreatitis were 1.6 (95% CI, 1.0-2.6; 4.3 events/10 000 person-years) for individuals with triglyceride levels of 89 mg/dL to 176 mg/dL (1.00 mmol/L-1.99 mmol/L), 2.3 (95% CI, 1.3-4.0; 5.5 events/10 000 person-years) for 177 mg/dL to 265 mg/dL (2.00 mmol/L-2.99 mmol/L), 2.9 (95% CI, 1.4-5.9; 6.3 events/10 000 person-years) for 366 mg/dL to 353 mg/dL (3.00 mmol/L-3.99 mmol/L), 3.9 (95% CI, 1.5-10.0; 7.5 events/10 000 person-years) for 354 mg/dL-442 mg/dL (4.00 mmol/L-4.99 mmol/L), and 8.7 (95% CI, 3.7-20.0; 12 events/10 000 person-years) for individuals with triglyceride levels greater than or equal to 443 mg/dL (≥5.00 mmol/L) (trend, P = 6 × 10⁻⁸). Corresponding HRs for myocardial infarction were 1.6 (95% CI, 1.4-1.9; 41 events/10 000 person-years), 2.2 (95% CI, 1.9-2.7; 57 events/10 000 person-

years), 3.2 (95% CI, 2.6-4.1; 72 events/10 000 person-years), 2.8 (95% CI, 2.0-3.9; 68 events/10 000 person-years), and 3.4 (95% CI, 2.4-4.7; 78 events/10 000 person-years) (trend, $P = 6 \times 10^{-31}$), respectively. The multivariable adjusted HR for acute pancreatitis was 1.17 (95% CI, 1.10-1.24) per 89 mg/dL (1 mmol/L) higher triglycerides. When stratified by sex, age, education, smoking, hypertension, statin use, study cohort, diabetes, body mass index (calculated as weight in kilograms divided by height in meters squared), alcohol intake, and gallstone disease, these results were similar with no statistical evidence of interaction.

CONCLUSIONS AND RELEVANCE: Nonfasting mild-to-moderate hypertriglyceridemia from 177 mg/dL (2 mmol/L) and above is associated with high risk of acute pancreatitis, with HR estimates higher than for myocardial infarction.

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Cut the fat: Putting the risks of hypertriglyceridemia into context

A brief response to "Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis"

In their article, Pedersen and colleagues present findings from their prospective cohort study on hypertriglyceridemia and its association with both acute pancreatitis and myocardial infarction.¹ With a median follow-up of 6.7 years (interquartile range, 4.0 to 9.4 years) among 116,550 "white individuals of Danish descent from the Danish general population"^{1(p1835)} selected randomly from two similar prospective studies (the Copenhagen City Heart Study and the Copenhagen General Population Study), this is a sizable study with respectable follow-up, even if generalizability of the findings might be at least somewhat limited. They rightly note "there is no consensus on a clear threshold above which triglycerides are associated with acute pancreatitis,"^{1(p1835)} and others have highlighted important issues with the evidence base.² Pedersen and colleagues also cite a review³ on triglycerides and cardiovascular disease, but here too the evidence is not entirely clear; the review only concludes evidence "is increasing"^{3(p633)} and recommends high-intensity statin therapy. The review also considers

the future potential of add-on triglyceride-lowering therapy for those already on a statin, pointing to two ongoing trials of ω -3 fatty acids ([REDUCE-IT](#) and [STRENGTH](#)). However, the currently-available evidence - particularly that with patient-relevant outcomes - does not support such a strategy for ω -3 fatty acids or other agents that can substantially lower triglycerides (such as fibrates and niacin).^{2,4,5}

Even if their study reflects an underlying truth, Pedersen and colleagues unfortunately demonstrate a relative inattention to absolute risks and the implications thereof. They devote a small amount of text to absolute risks and report absolute numbers in the figures, but they repeatedly state their findings show “high risk” for acute pancreatitis, a perspective seemingly driven by the magnitude of the hazard ratios (HRs). In their concluding statements, they even remark: “Mild-to-moderate hypertriglyceridemia at 177 mg/dL (2 mmol/L) and above is associated with high risk of acute pancreatitis in the general population, with HRs higher than for myocardial infarction.”^{1(p1841)}

When caring for individual patients, relative metrics such as HRs are most useful when appropriately applied to corresponding baseline absolute risks. Conversely, disproportionate focus on relative metrics or failure to adequately contextualize relative metrics with corresponding absolute risks is considerably less informative and can contribute to a distorted sense of reality. Even if one accepts research findings as being likely reflective of an underlying truth, one must always carefully appraise absolute risks to gain a finer appreciation of the quantitative implications of the research findings. This practice is still useful even if one finds weaknesses in methodology, as one can simply consider the estimates increasingly uncertain in a manner qualitatively proportional to the weaknesses in methodology. A tool customized for this study is available [here](#) (TinyURL: <http://tinyurl.com/JAMAIHypertrigcalctool>).

According to their own data, comparing the lowest triglyceride level group (<89 mg/dL or <1 mmol/L) to the highest triglyceride level group (\geq 443 mg/dL or \geq 5 mmol/L), one finds an absolute risk difference (ARD) for acute pancreatitis of 0.93% over 10 years if using the absolute numbers reported in Figure 1 to estimate absolute risks, and an ARD of 2.05% over 10 years (95% confidence interval [CI], 0.73% to 4.99%) if using the absolute risk in the lowest triglyceride level group and the multivariable-adjusted HR estimate for the highest triglyceride level group (HR 8.7; 95% CI, 3.7 to 20). Repeating this for myocardial infarction, one finds an ARD of 5.6% over 10 years or an ARD of 5.08% (95% CI, 3.00% to 7.73%) over 10 years. This demonstrates at least one reason why it is important to put relative metrics into context: Although the HRs for acute pancreatitis may be “higher than for myocardial infarction”,^{1(p1841)} the absolute risks and absolute risk differences are higher for myocardial infarction. Additionally, it is more informative to provide risk estimates in absolute terms than in relative terms. Indeed, as aforementioned, absolute risks give better insight into what research might mean for a patient if one accepts the findings as being reflective of an underlying truth. Unfortunately, [The New York Times](#)’ coverage of the study exacerbates the issue, with the only attempt to contextualize the relative metrics being a quote from one of the study’s authors. (Such mishandling of evidence is not uncommon in the media, but that is not the focus of this commentary. Including *The New York Times*’ coverage is not meant to single them out as uniquely bad or good in this regard; it simply serves as an example.) It is ultimately a disservice to say the risk of pancreatitis was 770% higher in patients with triglycerides \geq 443 mg/dL (\geq 5 mmol/L) compared to patients with triglycerides <89 mg/dL (<1 mmol/L) without contextualizing such a metric with absolute risks. More technically, and as discussed in the [tool](#), HRs are also not quite the same as relative risks.

Lastly, while management was not a focus Pedersen and colleagues’ article, sensible lifestyle changes should be emphasized wherever poor lifestyle factors exist. As for interventions beyond lifestyle changes, a medication that can reduce cardiovascular risk – such as a statin – might be instituted after shared decision-making concerning a person’s cardiovascular risk estimate; importantly, however, a

person's cardiovascular risk estimate is *not* dependent on triglyceride levels, and pharmaceutical intervention targeted at lowering triglycerides *per se* is *not* clearly supported by currently-available evidence examining cardiovascular, pancreatic, or other patient-relevant outcomes.

References

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