

University of Groningen

Normal fasting triglyceride levels and incident hypertension in community-dwelling individuals without metabolic syndrome

Szili-Torok, Tamas; Xu, Yuanxin; de Borst, Martin H.; Bakker, Stephan J.L.; Tietge, Uwe J.F.

Published in:
Journal of the American Heart Association

DOI:
[10.1161/JAHA.122.028372](https://doi.org/10.1161/JAHA.122.028372)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Szili-Torok, T., Xu, Y., de Borst, M. H., Bakker, S. J. L., & Tietge, U. J. F. (2023). Normal fasting triglyceride levels and incident hypertension in community-dwelling individuals without metabolic syndrome. *Journal of the American Heart Association*, 12(16), Article e028372. <https://doi.org/10.1161/JAHA.122.028372>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

RESEARCH LETTER

Normal Fasting Triglyceride Levels and Incident Hypertension in Community-Dwelling Individuals Without Metabolic Syndrome

Tamas Szili-Torok , MD; Yuanxin Xu , MSc; Martin H. de Borst , MD, PhD; Stephan J. L. Bakker , MD, PhD; Uwe J. F. Tietge , MD, PhD

Hypertension represents a highly relevant modifiable risk factor for all-cause death, cardiovascular disease, and chronic kidney disease, with a worldwide increasing prevalence and incidence.¹ Early identification of individuals prone to developing hypertension is essential to timely initiate lifestyle changes.¹ Thus far, elevated triglycerides ≥ 150 mg/dL are considered a risk factor for incident hypertension as part of the metabolic syndrome and as an indicator of insulin resistance and diabetes.² However, the association of triglycerides within the normal range with incident hypertension in the absence of the metabolic syndrome or diabetes is unclear. Therefore, the current study aimed to address this question in PREVENT (Prevention of Cardiovascular and End-Stage Renal Disease), a large contemporary general population cohort from the Northern Netherlands with a thorough long-term follow-up.

The data that support the findings of this study are available from the corresponding author upon reasonable request. Briefly, of 8592 initial PREVENT participants (approved by the medical ethics committee of the University Medical Center Groningen [MEC96/01/022], carried out according to the Declaration of Helsinki; all participants provided written informed consent),³ those with blood pressure $\geq 130/85$ mmHg, missing blood

pressure or triglyceride values, or incomplete hypertension follow-up were excluded ($n=2790$, no systematic differences with whole cohort). Furthermore, participants with increased triglycerides (>150 mg/dL) or metabolic syndrome at baseline (National Cholesterol Education Program's Adult Treatment Panel III report definition, 2004) were excluded, finally leaving 1749 eligible participants. Baseline blood pressure was measured on the nondominant arm in a semisupine position using the automated Dinamap XL Model 9300 device (Critikon, Tampa, FL) every minute for 15 minutes; the average of the last 3 measurements was calculated. Participants were left alone for the measurements.

Hypertension during follow-up was defined as initiation of antihypertensive medication (self-reported or hospital dispensing registry data) or physician diagnosis (office blood pressure measurement $>140/90$ mmHg). Triglycerides were determined enzymatically (Abbott Laboratories, Abbott Park, IL).

R version 4.1.2 (R Studio, RStudio Team, 2020, code: https://github.com/tamas875/research_methods) was used for statistical analyses. *P* values <0.05 were considered statistically significant. For baseline characteristics analyses, participants were divided into sex-stratified tertiles of fasting normal triglycerides. Statistical differences between tertiles were tested

Key Words: cholesterol ■ general population ■ hypertension ■ lipids ■ triglycerides

Correspondence to: Uwe J. F. Tietge, MD, PhD, Division of Clinical Chemistry, Department of Laboratory Medicine (LABMED), H5, Alfred Nobels Alle 8, Karolinska Institutet, S-141 83 Stockholm, Sweden. Email: uwe.tietge@ki.se

This manuscript was sent to Shakia T. Hardy, PhD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 3.

© 2023 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

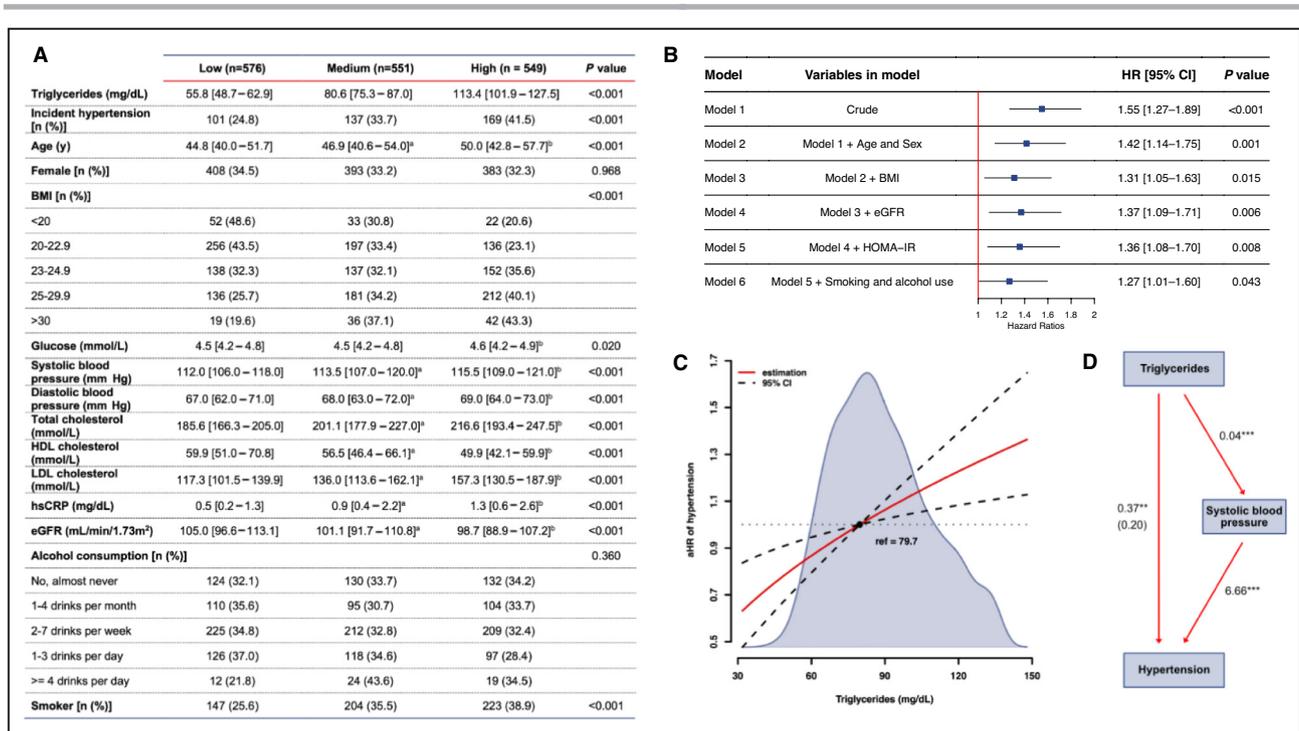


Figure. Normal fasting triglycerides and incident hypertension.

A, Baseline characteristics of the participants across sex-stratified tertiles of normal fasting triglycerides. Differences between tertiles were tested using the Kruskal–Wallis test for skewed variables (given as median [interquartile range]) and χ^2 test for categorical variables (given as number [percentage]). Post hoc analyses were performed using Dunn's test, and *P* values were adjusted with the Benjamini–Hochberg method. *Tertile significantly different from the first tertile ($P < 0.05$) †Tertile significantly different from the second tertile ($P < 0.05$). **B**, Stepwise Cox regression analysis of triglycerides adjusted for several potential confounders. Model 1, crude analysis; model 2, adjusted for age and sex; model 3, model 2 plus BMI; model 4, model 3 plus eGFR; model 5, model 4 plus HOMA-IR; model 6, model 5 plus alcohol use and smoking. In model 1 (crude analysis) triglycerides were stratified to meet the proportional hazards assumption. **C**, Adjusted hazard ratio of hypertension incidence at different triglyceride levels (mg/dL). Hazard ratios were obtained by Cox regression analysis. **D**, Results of the mediation analysis for systolic hypertension as mediator between triglycerides and incident hypertension. The age- and sex-adjusted OR between triglycerides and hypertension was determined by logistic regression. Next, systolic blood pressure was added to the model, resulting in a considerably lower and nonsignificant OR (shown in brackets). Subsequently, the regression coefficient between triglycerides and systolic blood pressure was obtained by linear regression. Finally, the OR between systolic blood pressure and incident hypertension was determined. ** $P < 0.01$; *** $P < 0.001$. aHR indicates adjusted hazard ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and OR, odds ratio.

using the χ^2 test for categorical, Kruskal–Wallis test for skewed, and 1-way ANOVA for normally distributed variables (Q-Q plots). The continuous relationship between normal triglycerides and incident hypertension was assessed by Cox regression adjusted for several potential confounders. If the proportional hazards assumption (Schoenfeld residuals) was not met, the covariate showing nonproportional hazard was stratified. Mediation analyses were done to explore whether systolic blood pressure is a mediator between triglycerides and incident hypertension.

During a median (interquartile range) follow-up of 11.2 (8.3–11.9) years, 407 participants (23.3%) developed hypertension. Incident hypertension was higher, with increasing tertiles of baseline triglycerides ($P < 0.001$; Figure [A]). Furthermore, participants with higher triglycerides were older ($P < 0.001$), had higher

blood pressure ($P < 0.001$), increased total and low-density lipoprotein cholesterol ($P < 0.001$), lower high-density lipoprotein cholesterol ($P < 0.001$), more inflammation ($P < 0.001$), and worse kidney function ($P < 0.001$). Participants with higher triglycerides were more likely to be active smokers ($P < 0.001$) and had higher body mass index ($P < 0.001$).

Cox regression (Figure [B]) showed that normal fasting triglycerides were significantly associated with incident hypertension in models including potential confounders (crude model: hazard ratio, 1.55 [95% CI, 1.27–1.89]; $P < 0.001$). Interaction tests showed no significant interaction between sex and fasting triglycerides ($P = 0.942$). Visualizing the relationship between baseline normal fasting triglycerides and incident hypertension (Figure [C]) indicated that increasing triglyceride levels resulted in a continuously increasing

adjusted hazard ratio. Mediation analysis revealed that systolic hypertension was a full mediator between triglycerides and incident hypertension (Figure [D]).

This study demonstrates that in the metabolic syndrome-free general population normal triglyceride levels are prospectively positively associated with incident hypertension. Interestingly, this association extended throughout the whole range of normal triglycerides. These data expand on previous work that elevated triglycerides in prevalent metabolic syndrome or diabetes are a risk factor for hypertension.² Of note, biomarkers frequently associated with the metabolic syndrome, such as high-density lipoprotein cholesterol, total cholesterol, blood pressure, and body mass index, also exhibited a strong correlation to triglycerides within the currently handled normal range. These results suggest that metabolic syndrome could be viewed as a continuous condition and that virtually every participant might benefit from triglyceride lowering through lifestyle modifications by, for example, exercising, increasing legume and fruit intake, and avoiding consumption of beverages or snacks with high sugar content.⁴

PREVEND is a well-characterized large general population cohort; however, it includes predominantly White participants (95.7%), warranting confirmation in other populations. Another potential limitation is that only a single fasting measurement of triglycerides was taken at inclusion. Potentially, nonfasting triglycerides might provide different or additive information.

In conclusion, normal fasting triglycerides are prospectively associated with incident hypertension in the metabolic syndrome-free general population throughout the full range of values. Together with our previous data that normal triglycerides associate with incident insulin-resistant diabetes,⁵ these results indicate that in clinical practice every individual should be encouraged to maintain as low as possible triglyceride levels.

Further, analogous to the recent lowering of the upper normal blood glucose value, a similar approach might be worth considering with respect to triglycerides.

ARTICLE INFORMATION

Received October 2, 2022; accepted June 5, 2023.

Affiliations

Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands (T.S.-T., Y.X., M.H.d.B., S.J.L.B.); Division of Clinical Chemistry, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden (U.J.F.T.); and Clinical Chemistry, Karolinska University Laboratory, Karolinska University Hospital, Stockholm, Sweden (U.J.F.T.).

Acknowledgments

Dr Szili-Torok: data acquisition, analysis, and interpretation; and drafting of the manuscript. Xu: data acquisition and analysis. Dr de Borst: data acquisition and interpretation, and critical revision of the manuscript. Dr Bakker: data acquisition and interpretation, and critical revision of the manuscript. Dr Tietge: conception and design of the study, data interpretation, and drafting of the manuscript.

Sources of Funding

This work was supported by the Center for Innovative Medicine (CIMED, FoUI-963 234, to Dr Tietge).

Disclosures

None.

REFERENCES

- Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cifková R, Dominiczak AF, Grassi G, Jordan J, Poulter NR, Rodgers A, et al. Hypertension. *Nat Rev Dis Primers*. 2018;4:18014. doi: [10.1038/nrdp.2018.14](https://doi.org/10.1038/nrdp.2018.14)
- Laaksonen DE, Niskanen L, Nyyssönen K, Lakka TA, Laukkanen JA, Salonen JT. Dyslipidaemia as a predictor of hypertension in middle-aged men. *Eur Heart J*. 2008;29:2561–2568. doi: [10.1093/eurheartj/ehn061](https://doi.org/10.1093/eurheartj/ehn061)
- Jia C, Anderson JLC, Gruppen EG, Lei Y, Bakker SJL, Dullaart RPF, Tietge UJF. High-density lipoprotein anti-inflammatory capacity and incident cardiovascular events. *Circulation*. 2021;143:1935–1945. doi: [10.1161/CIRCULATIONAHA.120.050808](https://doi.org/10.1161/CIRCULATIONAHA.120.050808)
- Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. *Eur Heart J*. 2020;41:99–109c. doi: [10.1093/eurheartj/ehz785](https://doi.org/10.1093/eurheartj/ehz785)
- Szili-Torok T, Bakker SJL, Tietge UJF. Normal fasting triglyceride levels and incident type 2 diabetes in the general population. *Cardiovasc Diabetol*. 2022;21:111. doi: [10.1186/s12933-022-01530-8](https://doi.org/10.1186/s12933-022-01530-8)