Appendices

LETTER TO THE EDITOR

RESPONSE REGARDING ARTICLE:"THYROID FUNCTION AND THE RISK OF ATHEROSCLEROTIC CARDIOVASCULAR MORBIDITY AND MORTALITY: THE ROTTERDAM STUDY"

Arjola Bano, Robin P. Peeters, Maryam Kavousi
Adapted from Circ Res. 2018;122(3):e18

We appreciate the comments by Drs. Zhao and Schooling regarding our recent publication.[1] In this study, we showed that higher circulating free thyroxine levels are associated with an increased risk of atherosclerosis throughout its full spectrum.

Zhao and Schooling argue that our observed associations are not supported by a Mendelian Randomization (MR) study, which found no evidence of an association between thyroid function and ischemic heart disease.[2] The following considerations need to be taken into account with regard to this study. First, the MR study focused on coronary artery disease. However, there are no MR studies, to our knowledge, on thyroid function and atherosclerotic cardiovascular disease. Second, the MR approach assumes that genetic variants determine the exposure. Still, only a limited number of genetic variants for free thyroxine have been identified, while a large proportion of thyroid function heritability remains unexplained. Third, the possibility of developmental compensation (ie, canalization) and pleiotropic effects of genetic variants cannot be excluded. Taken together, the current lack of genetic evidence does not rule out a potential effect of thyroid function on atherosclerotic cardiovascular disease.

We agree with the authors that we cannot prove a causal relationship due to the observational character of our study. However, the biological plausibility of our findings, the temporal relationship of the exposure with atherosclerotic events, and the various sensitivity analyses accounting for reverse causation strongly suggest an effect of thyroid function on atherosclerotic cardiovascular morbidity and mortality.[1] Moreover, our findings are consistent with the results of the randomized controlled trial cited by Zhao and Schooling.[3] This trial investigated the effects of dextrothyroxine treatment in patients with a history of myocardial infarction. The proportions of all-cause deaths, deaths from cardiovascular disease, deaths from coronary heart

disease and non-fatal recurrent myocardial infarctions were higher in the treatment arm than in the placebo arm of the trial, leading to a discontinuation of the trial after 36 months. In line, our study shows that higher free thyroxine levels are associated with an increased risk of atherosclerotic cardiovascular mortality, particularly among subjects with preexisting atherosclerotic cardiovascular disease.

Furthermore, Zhao and Schooling hypothesize that androgens can confound or mediate the association of thyroid function with atherosclerotic cardiovascular outcomes. This is an intriguing hypothesis, though the association of testosterone with atherosclerotic cardiovascular outcomes remains largely unclear.[4] To date, randomized controlled trials investigating the effects of testosterone treatment on major cardiovascular events have yielded conflicting results.[4] We had data available on testosterone concentrations in more than 99% of participants. After adding testosterone to our models, the association of thyroid function with atherosclerotic cardiovascular outcomes remained unchanged or became slightly stronger. Sex-specific analyses provided consistent findings before and after additional adjustments for testosterone. These data suggest that the association of thyroid function with atherosclerosis is independent of testosterone concentrations.

In the future, large MR studies are warranted to examine the association of genetically predicted thyroid function with atherosclerotic cardiovascular outcomes. Further investigations are also needed to elucidate the exact mechanisms linking thyroid function to atherosclerosis.

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LETTER TO THE EDITOR
LIFE-EXPECTANCY OF LOW-NORMAL THYROID FUNCTION: REPLY

Arjola Bano, Robin P. Peeters, Oscar H. Franco
Adapted from JAMA Intern Med. 2018;178(3):437-438

We would like to thank Dr. Inoue and colleagues for their interest in our recent publication.[1] As suggested by Inoue and colleagues, we now provide some additional information about our analyses. Our life expectancy calculations utilized age-adjusted hazards and age-specific mortality rates, based on the data of individuals at different ages and different health states. In the third transition (ie, mortality among those with cardiovascular disease [CVD]), stratified analyses among participants who acquired CVD during the study period and participants who already had a history of CVD at baseline consistently showed that high-normal thyroid function is linked to a higher mortality risk than low-normal thyroid function. In addition, sensitivity analyses restricting the follow-up time to different lengths (ie, 6, 8, 10 years of follow-up) yielded similar results. These data point towards a persistent effect of thyroid hormones on mortality risk across time.

Both the first and the second transition included participants who were free of CVD at baseline. Participants in the first transition (ie, incident CVD) were followed up until the occurrence of CVD events, whereas those in the second transition (ie, mortality among those without CVD) were followed up until they died. As a consequence, person years at risk were different between the two transitions.

We agree with Dr. Inoue and colleagues that low thyroid function has a negative impact on cardiovascular health. According to a large meta-analysis from the Thyroid Studies Collaboration, patients with subclinical hypothyroidism and thyrotropin levels above 10 mIU/L have an increased risk of coronary heart disease.[2] However, it is unclear to what extent these deleterious effects can be extended to lower thyrotropin levels. Future studies aiming to define the optimal reference ranges of thyrotropin and free thyroxine are warranted. Also, adequately powered randomized clinical trials focusing on the treatment of subclinical hypothyroidism in relation to CVD need to provide more robust evidence.

Our study showed that at the age of 50 years, individuals with low-normal thyroid function live longer than those with high-normal thyroid function. This is in line with other studies performed in middle-aged and older adults, suggesting that the risk of CVD and mortality increases from low-normal to high-normal thyroid function.[3,4] Such findings, however, may not be generalizable to younger populations.

We concur with Dr. Inoue and colleagues that low-normal thyroid function has been linked to metabolic syndrome. Our results, however, did not materially change after accounting for metabolic syndrome components, including diabetes mellitus, blood pressure, body mass index and lipid levels. Other factors beyond metabolic syndrome and its components therefore likely explain our findings. Within the reference range of thyroid function, differences in longevity can reflect differences in the risk of adverse outcomes. So far, lower thyrotropin and higher free thyroxine levels within the euthyroid range have been prospectively linked to an increased risk of atrial fibrillation, atherosclerotic CVD, heart failure and dementia, which are all associated with an increased risk of mortality.[4-6]

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LIST OF PUBLICATIONS AND MANUSCRIPTS

Bano A*, Chaker L*, Plompen EP, Hofman A, Dehghan A, Franco OH, Janssen HL, Darwish Murad S, Peeters RP. Thyroid function and the risk of nonalcoholic fatty liver disease: The Rotterdam Study. *J Clin Endocrinol Metab.* 2016;101(8):3204-3211.

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Asllanaj E, **Bano A**, Glisic M, Jaspers L, Ikram MA, Laven JSE, Vőlzke H, Muka T, Franco OH. Age at natural menopause and life expectancy with and without type 2 diabetes. *Menopause - The Journal of The North American Menopause Society 2018*

Bano A, Chaker L, de Maat MPM, Atiq F, Kavousi M, Franco OH, Mattace-Raso FUS, Leebeek FWG, Peeters RP. Thyroid function and cardiovascular disease: the mediating role of coagulation factors. *Submitted*

Bano A*, Gan E*, Addison C, Narayanan K, Weaver JU, Tsatlidis V, Razvi S. Age may influence the impact of TRAbs on thyroid function and relapse-risk in patients with Graves' disease. *Submitted*

Nano J, Pulido T, **Bano A**, Brahimaj A, Alferink LJM, Kraja B, Darwish Murad S, Dehghan A, Franco OH, Muka T. Fatty liver index and risk of diabetes, cardiovascular disease and mortality: The Rotterdam Study. *Submitted*

Bano A, Chaker L, Mattace-Raso FUS, Peeters RP, Franco OH. Association of thyroid function with life expectancy with and without non-communicable diseases: The Rotterdam Study. *Manuscript in preparation*

Bano A, et al. Thyroid function and the risk of fibrosis of the liver, lung, and heart: A systematic review of human studies. *Manuscript in preparation*

** Denotes equal contribution within a manuscript*

ABOUT THE AUTHOR

Arjola Bano was born on 21 October, 1985 in Kucove, Albania. In 2004, she graduated cum laude from the General High School in her home town. She started studying medicine at the University of Tirana in the same year and obtained her medical degree in 2010. Furthermore, she completed 4 years of residency in the Department of Internal Medicine, University Hospital Centre "Mother Teresa" of Tirana, and obtained the degree "Specialist in Internal Medicine" from the University of Tirana. As part of her medical training in Internal Medicine, Arjola was awarded a scholarship from the "Agence Universitaire de la Francophonie" to study Endocrinology at the University Hospital Center of Bicetre in Paris. In August 2014, Arjola was awarded a scholarship from "Erasmus Western Balkans" to pursue a Master of Science program in Clinical Epidemiology at the Netherlands Institute of Health Sciences, Erasmus University, Rotterdam (2014-2015). After obtaining her master degree, Arjola completed a Doctor of Science program in Clinical Epidemiology at the Netherlands Institute of Health Sciences (2015-2016). These studies in Clinical Epidemiology were combined with a PhD program at the Departments of Internal Medicine and Epidemiology of Erasmus Medical Center, under the supervision of Prof. Robin Peeters, Prof. Oscar Franco, Prof. Francesco Mattace-Raso and Dr. Layal Chaker. During her PhD training, Arjola performed multiple research projects that were focused on the role of thyroid function on cardiometabolic health and general health. Her research work is encompassed in this PhD thesis entitled "Thyroid function, cardiometabolic health and general health". In 2018, Arjola was awarded a fellowship grant from the European Thyroid Association to perform further research at the Cardiovascular Research Centre, Institute of Genetic Medicine, Newcastle University.

PHD PORTFOLIO

PhD student	**Arjola Bano**
Erasmus MC Department	Internal Medicine, Academic Center for Thyroid Diseases, Epidemiology
Promotors	Prof. Dr. Robin P. Peeters Prof. Dr. Oscar H. Franco Prof. Dr. Francesco U.S. Mattace-Raso
Co-promotor	Dr. Layal Chaker

Training	Year	ECTS
Master of Science in Clinical Epidemiology, NIHES, Erasmus Medical Center, Rotterdam, the Netherlands		
Research period Master of Science	2014-2015	33.5
General courses		
Study Design	2014	4.3
Biostatistical Methods I: Basic Principles	2014	5.7
Clinical Epidemiology	2014	5.7
Methodologic Topics in Epidemiologic Research	2014	1.4
Biostatistical Methods II: Classical Regression Models	2014	4.3
Principles of Research in Medicine	2014	0.7
Cohort studies	2014	0.7
Case-control studies	2014	0.7
Logistic Regression	2015	1.4
Causal Mediation Analysis	2015	0.7
Primary and Secondary Prevention Research	2015	0.7
Methods of Public Health Research	2014	0.7
Markers and Prediction Research	2015	0.7
Health Economics	2014	0.7
Introduction to Global Public Health	2015	0.7
The Practice of Epidemiologic Analyses	2015	0.7
Fundamentals of Medical Decision Making	2015	0.7
Advanced courses		
Planning and Evaluation of Screening	2015	1.4
Public Health in Low and Middle Income Countries	2015	3.0
Skill courses		
English Language	2014	1.4
Introduction to Medical Writing	2015	1.1
Courses for the Quantitative Researcher	2015	1.4

Doctor of Science in Clinical Epidemiology, NIHES, Erasmus Medical Center, Rotterdam, the Netherlands

Research period Doctor of Science	2015-2016	62.3
Bayesian Statistics	2016	1.4
Conceptual Foundation of Epidemiologic Study Design	2016	0.7
Causal Inference	2016	0.7
History of Epidemiologic Ideas	2016	0.7
Advances in Epidemiologic Analysis	2016	0.4
Causal Mediation Analysis	2016	0.7
Principles of Epidemiologic Data-analysis	2016	0.7
Missing Values in Clinical Research	2016	0.7
Women's Health	2016	0.9
Health Services: Research and Practice	2016	0.9
Introduction to Psychology in Medicine	2016	1.4

Academic Courses

Research Integrity	2017	0.3

Conferences – Oral presentations

Dutch Endocrine Meeting, Noordwijk, the Netherlands *Thyroid function and the risk of nonalcoholic fatty liver disease*	2016	0.7
Research Meeting of Internal Medicine, Rotterdam, the Netherlands *Low thyroid function linked to nonalcoholic fatty liver disease*	2016	0.7
Dutch Endocrine Meeting, Noordwijk, the Netherlands *Low-normal thyroid function associated with increased life expectancy: The Rotterdam Study*	2017	0.7
Endocrine Society Annual Meeting, Orlando, Florida (press released) *People with higher thyroid hormone levels may be at greater risk for atherosclerosis*	2017	0.7
Research Meeting of Internal Medicine, Rotterdam, the Netherlands *Low-normal thyroid function linked to an increased life expectancy*	2017	0.7
European Thyroid Association Annual Meeting, Belgrade, Serbia (Topic Highlights Session) *Association of thyroid function with life expectancy with and without cardiovascular disease*	2017	0.7
Dutch Endocrine Meeting, Noordwijk, the Netherlands *Thyroid function and cardiovascular outcomes: Is there a mediating role of coagulation?*	2018	0.7

Conferences – Poster presentations

Science Days Internal Medicine, Antwerp, Belgium *Thyroid function and the risk of nonalcoholic fatty liver disease*	2016	0.7
Science Days Internal Medicine, Antwerp, Belgium *Low-normal thyroid function associated with increased life expectancy*	2017	0.7
Science Days Internal Medicine, Antwerp, Belgium *Thyroid function and cardiovascular outcomes: Is there a mediating role of coagulation?*	2018	0.7

Seminars and meetings

Thyroid Lab Meetings	2015-2018	1.0
Cardiovascular group Meetings	2015-2018	1.0
Seminars at the Department of Epidemiology	2015-2018	1.0
2020 Epidemiology Meetings	2015-2018	1.0
Dutch Thyroid Club Annual Meetings, Amsterdam	2015-2017	0.7

Other Activities

Peer Reviews for JAMA, European Journal of Epidemiology	2017-2018	0.5

Grants

ERAWEB Scholarship for a Master of Science in Clinical Epidemiology	2014
Travel Grant “Erasmus Trustfonds” for ENDO 2017	2017
European Thyroid Association “Exchange fellowship grant”	2018

"The more one is able to leave one's cultural home, the more easily is one able to judge it, and the whole world as well, with the spiritual detachment and generosity necessary for true vision. The more easily, too, does one assess oneself and alien cultures with the same combination of intimacy and distance"

Edward Said

WORDS OF GRATITUDE

This PhD trajectory has been one of the most interesting experiences of my life, which has enriched me not only at an academic level but also at a personal level. Despite the challenges that I encountered throughout this adventurous journey, my love for research and the considerable support of many people kept me going forward. Although it is impossible to mention everyone, I am extremely grateful to all those who have directly or indirectly supported me throughout this trajectory.

To my mentors, colleagues, and collaborators

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I would like to express my highest considerations to the committee members. Dear members of the *inner committee*, *Prof. Ikram, Prof. Razvi, and Prof. Smit;* Dear *members of the plenary committee, Dr. Kavousi, Dr. van Heemst, and Prof. van der Lelij*. I greatly appreciate your time and expertise in the assessment of this thesis.

I would like to thank all *coauthors and collaborators* from the Academic Center for Thyroid Diseases, Department of Internal Medicine, Section of Geriatric Medicine, Department of Epidemiology, Department of Hematology, Department of Radiology, Department of Neurology, Department of Neuroscience, Department of

Gastroenterology and Hepatology, for the valuable contribution. Special thanks to *Dr. Maryam Kavousi*, for the insightful discussions on atherosclerosis; *Dr. Klodian Dhana*, for the useful input on the life tables project; and *Dr. Abbas Dehghan*, for the valuable methodological advices.

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I am grateful to the *researchers of the Cardiovascular Research Centre in Newcastle University* for kindly welcoming me in Newcastle. Dear *Dr. Salman Razvi*, I could not have had a better supervisor for my exchange project. Thank you for your kindness and the insightful discussions on thyroid function. I am so glad that you are travelling from the United Kingdom to attend my PhD defense. Dear *Prof. Simon Pearce and Dr. Earn Gan*, thank you for the feedback during the research meetings, and the memorable trips at Farne Islands and Craigside.

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the technical support; *Solange and Andrea*, for the help with my residence permit applications; *Mirjam, Anneke, and Caroline*, for the administrative assistance.

To Victoria Horkan

I am honored to have the painting of *Victoria Horkan* as the cover of my thesis. Beyond the underlying symbolic, I also perceive this colorful butterfly as a wonderful source of strength and positive energy.

To my friends and family

During my stay in Rotterdam, I have had the chance to meet many interesting people from all over the world. *Aline, Giorgia, Laura, Alexandra, Rocio, Natasa, Dory, Amerigo, Ghassan, Paul, Gaby, and all other international friends*, thank you for allowing me to embrace cultural diversity, and for making me realize how much we have in common. Through you, I have also discovered the beauty of the countries you come from. *Aline*, since we met for the first time, I knew I had found a friend for life. *Laura and Alexandra*, I have so many good memories with you, and I am extremely glad that you are my paranymphs.

I further thank *all the Albanian friends* that I have met in Rotterdam, who brought me a piece of my warm country in the Netherlands. I will always remember the beautiful moments we have spent together. *Bisela and Sigi,* I have enjoyed being with you in many lectures, seminars, and leisure activities. Many thanks to *Anisa, Klodian, and little Mikel*, for making my Saturdays in Rotterdam very pleasant; *to Lela*, for her kindness and continuous support*;* and to *Jugena*, for always encouraging and cheering me up.

Being far from my beloved family was one of the major challenges of this journey. I thank my *aunt, uncles, cousins, and their families*, for their affection. *Mami, Babi, and Elisa,* thank you for understanding and supporting me in any decision that I have made in my life. Your immense unconditional love has kept me going forward. Furthermore, I would like to express my sincere appreciation to *Elton`s family*.
Dear Elton, it is amazing how close we have become over these years. I am blessed to be surrounded every day by your absolute optimism, positive energy, and love.