The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 1, e429–e431
https://doi.org/10.1210/clinem/dgab525
Commentary

Commentary

A Deeper Understanding of the Causal Relationships Between Thyroid Function and Atrial Fibrillation

Aleksander Kuś,[1] Alexander Teumer,[2,3] and Marco Medici[4,5]

[1]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland; [2]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany; [3]DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany; [4]Academic Center for Thyroid Diseases, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; and [5]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

ORCiD numbers: 0000-0001-5422-6900 (A. Kuś); 0000-0002-8309-094X (A. Teumer); 0000-0002-7271-7858 (M. Medici).

Abbreviations: AF, atrial fibrillation; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; TSH, thyrotropin.

Received: 14 June 2021; Editorial Decision: 13 July 2021; First Published Online: 19 July 2021; Corrected and Typeset: 16 August 2021.

Key Words: Thyroid-stimulating hormone, atrial fibrillation, Mendelian randomization, height

Thyroid hormones are highly pleiotropic and even minor variations in thyroid function have been associated with various adverse clinical outcomes in observational studies. This has opened up discussions whether mild (subclinical) thyroid dysfunction should be treated and whether reference ranges for thyroid function tests should be adapted. However, observational studies are prone to various sources of bias, including residual confounding, reverse causality, and selection bias, which can affect their results and disrupt their interpretation. It is therefore key to first assess whether the reported associations are causal or not. While most of the reported associations have not been verified by randomized controlled trials or experimental studies, Mendelian randomization (MR) is a well-established and widely used method to investigate causality. Its fundamental principle is that genetic variants which alter an exposure that is causal for the outcome of interest should also be associated with this outcome to the extent corresponding to their effects on the exposure (1). In this way, genetic variants are used as proxies to evaluate the causal effect of an exposure (eg, thyroid function) on the outcome of interest. They draw from the fact that genetic variants segregate randomly from parents to offspring, which can be compared with the randomization applied in clinical trials and allows potential confounding to be overcome. However, this approach requires several assumptions: the genetic variants used as instruments in MR analyses have to be associated with the exposure, they have to be independent of confounders of the exposure–outcome relationship, and their effects on the outcome of interest have to be mediated solely by the exposure under study. Consequently, any so-called horizontal pleiotropic variants should be excluded as they can bias the results of a MR analysis (1).

Up to 65% of the interindividual variation in thyroid function is determined by genetic factors (2, 3). Recent large-scale meta-analyses of genome-wide association studies on thyroid function significantly increased the number of genetic variants associated with normal-range

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

thyrotropin (TSH) and free thyroxine levels, which paved the way for well-powered MR studies (3, 4). Indeed, various MR studies on thyroid function provided evidence for causal effects on several classical thyroid hormone dependent outcomes, such as atrial fibrillation (AF), blood pressure, and serum cholesterol levels, which confirms that this method is truly effective in detecting causality (5, 6).

Besides providing evidence for causality, multivariable MR (MVMR) analyses can also elucidate the pathophysiological mechanisms behind the observed association by simultaneously testing the effects of multiple factors on the outcome of interest. In brief, factors that attenuate the effect of the analyzed exposure on the tested outcome in a MVMR analysis are considered as mediators for the causal relationship between these 2 traits. Using this approach, AF was identified as a mediator for the causal association between variation in normal-range thyroid function and stroke (7).

In the current study, Shi et al. (8) used the MVMR approach to discover mediators for the causal relationship between variation in normal-range thyroid function and AF risk, next to the direct effects of thyroid hormone on the heart. For this, several physiologically plausible mediators were assessed in their study (eg, blood pressure, heart rate, and various cardiac structure parameters). Correction for height attenuated the effect of genetically predicted TSH levels on AF risk from –0.12 (±0.02) to –0.06 (±0.02) change in log-transformed odds ratio (±standard error) per a standard deviation increase in TSH. In this way, height was identified as the major independent mediator in the causal association between variation in normal-range thyroid function and AF risk (8). This finding is in line with well-documented effects of thyroid function on childhood growth as well as with previous observational studies showing that height positively correlates with AF risk. Importantly, the authors subsequently showed that height was not a mediator in the relation between thyroid function and AF when analyses were restricted to only those TSH-associated genetic variants which are also related to autoimmune thyroid disease. This supports the biological plausibility of their findings, since autoimmune thyroid disease usually presents in adulthood far after the completion of growth (8). The fact that the effects of genetically determined thyroid function on AF risk are partly mediated by height is not only interesting from a pathophysiological point of view, but also from a clinical perspective: as height is determined in early life, it is likely that correction of thyroid function in later life will not fully reverse the effects of variation in thyroid function on AF risk described in observational studies.

This should be taken into account when weighing potential benefits and drawbacks of treating subclinical variations in thyroid function. Since well-powered randomized controlled trials will require a long follow-up period and a large group of participants to detect the effects of minor variations in thyroid function on long-term complications such as AF risk, the data on causality derived from MR studies are likely to be the only relevant data available in the near future. For the height-independent part of the effects of thyroid function on AF, future studies should clarify whether a certain deviation in thyroid function due to inherited genetic variants (lifetime exposure) has the same effect on AF risk as a similar nongenetically determined (more sudden) shift in thyroid function.

In conclusion, the study by Shi et al. (8). illustrates how a high-quality MR study followed by comprehensive sensitivity analyses and an in-depth critical analysis of findings can be a valuable and effective tool that not only allows to assess causality, but also improves our understanding of underlying modifiable and nonmodifiable pathways, with potential clinical implications. Given the pleiotropic nature of many other hormones, similar robust approaches should also be used in other endocrine fields.

Additional Information

Correspondence: Marco Medici, MD, PhD, MSc, Room Rg526, Academic Center for Thyroid Diseases, Department of Internal Medicine and Department of Epidemiology, Erasmus Medical Center, Dr Molewaterplein 50, 3015 GE, Rotterdam, The Netherlands. Email: m.medici@erasmusmc.nl.

Disclosure Summary: Nothing to disclose.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;**362**:k601.
2. Medici M, Peeters RP, Teumer A, Taylor P. The importance of high-quality Mendelian randomisation studies for clinical thyroidology. *Lancet Diabetes Endocrinol*. 2019;**7**(9):665-667.
3. Kus A, Chaker L, Teumer A, Peeters RP, Medici M. The genetic basis of thyroid function: novel findings and new approaches. *J Clin Endocrinol Metab*. 2020;**105**(6):1707-1721.
4. Teumer A, Chaker L, Groeneweg S, et al.; Lifelines Cohort Study. Genome-wide analyses identify a role for SLC17A4 and AADAT in thyroid hormone regulation. *Nat Commun*. 2018;**9**(1):4455.
5. Ellervik C, Roselli C, Christophersen IE, et al. Assessment of the relationship between genetic determinants of thyroid function and atrial fibrillation: a mendelian randomization study. *JAMA Cardiol*. 2019;**4**(2):144-152.
6. Kuś A, Marouli E, Del Greco M F, et al. Variation in normal range thyroid function affects serum cholesterol levels, blood pressure, and type 2 diabetes risk: a Mendelian randomization study. *Thyroid*. 2021;**31**(5):721-731.

7. Marouli E, Kus A, Del Greco MF, et al. Thyroid function affects the risk of stroke via atrial fibrillation: a Mendelian randomization study. *J Clin Endocrinol Metab*. 2020;**105**(8):2634-2641.

8. Shi M, Manouchehri AM, Shaffer CM, et al. Genetic thyroid stimulating hormone regulation of atrial fibrillation risk is mediated through an effect on height. *J Clin Endocrinol Metab*. 2021;**106**(7):2124-2132.