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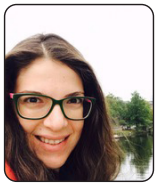
Abstract



Mendelian Randomization analyses reveal a causal effect of thyroid function on cardiovascular risk factors and diseases

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Abstract:

Despite progress in prevention and treatment over the past two decades, cardiovascular disorders remain a leading cause of mortality worldwide. Several observational studies suggest that even minor variation in thyroid function is associated with atherosclerotic cardiovascular disease, type 2 diabetes (T2D), hypertension, dyslipidaemia, and obesity. This raises the question as to whether common forms of mild thyroid dysfunction need treatment to prevent such complications. Through two-sample Mendelian randomization approaches, we investigated whether the relationship between thyroid function (interrogated through variation in reference range TSH and FT4, subclinical hypo- and hyperthyroidism, Hashimoto's Disease (HD) and Graves' disease) and cardiometabolic risk is causal, and possible mediation pathways underlying it. Using both published GWAS results and data from the UK Biobank, we show that one standard deviation (SD) increase in TSH levels causes a 5% decrease in the risk of stroke (OR=0.95, 95% CI= 0.91 to 0.99). Multivariable MR analyses indicated that this effect is mediated through atrial fibrillation (AF). While normal range thyroid function is not associated with Coronary Artery Disease (CAD), HD was associated with a 7% increased risk of CAD (OR=1.07, 95% CI= 1.01 to 1.13). The effect of HD on CAD risk appears to be mediated via body mass index (BMI). Looking at cardiovascular risk factors, a one SD increase in TSH levels was causally associated with: an increase of 0.05 SD units in total cholesterol serum levels (β=0.05, 95% CI= 0.02 to 0.08), a 0.03 SD unit increase in low-density lipoprotein (β=0.03, 95% CI= 0.003 to 0.02), and a 0.31 mmHg decrease in pulse pressure (PP) (β=-0.31, 95% CI= -0.54 to -0.08). In line with these findings, subclinical hyperthyroidism is causally associated with increased PP (β=0.15, 95% CI= 0.05 to 0.25). There is no evidence for a causal association between normal range FT4 levels and the tested outcomes. These results establish that minor variation in normal range thyroid function can be a novel modifiable risk factor for stroke through its effect on AF. Furthermore, variation in thyroid function can affect cardiovascular risk via its effects on cholesterol levels and blood pressure. These findings pave the way to consider future adjustment of thyroid function in managing patients' risk of stroke.

Biography:

Dr Marouli's research interests lie at the interface of genetics, bioinformatics and statistics, in order to achieve a better understanding of human biology and disease prediction with the use of "Big Data". Her work focuses on using human genetics to identify genes that influence common diseases and quantitative traits, including height and adiposity. Dr Marouli implements novel computational methods, including machine learning, to gain biological insights from human genetic and phenotypic data. She has a leading role in the large international consortium (GIANT) that has discovered almost all of the genetic variants that are known to influence human height and obesity related traits. Dr Marouli has also leading work and contributions in global consortia (GLGC, CHARGE CARDIoGRAMplusC4D) for complex traits and diseases.In addition to gene discovery efforts, Dr Marouli is also interested in genetic-epigenetic approaches to complex phenotypes. Dr Marouli is focusing on the genetics of thyroid disease. Her recent work integrates the use of genetic data and a battery of state of the art approaches, for causal inference and mendelian randomisation, to elucidate the genetic interplay between risk factors and disease.

Publication of speakers:

1. Cooper DS, Biondi B, et al. Subclinical thyroid disease. Lancet. 2012;379:1142–1154. doi: 10.1016/S0140-6736(11)60276- 6.
2. Chaker L, et al. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis. J. Clin. Endocrinol. Metab. 2015;100:2181–2191. doi: 10.1210/jc.2015-1438.
3. Collet TH, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch. Intern. Med. 2012;172:799–809. doi: 10.1001/archinternmed.2012.402.

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