Genetic analysis technique finds missing link between thyroid function and lipid profile

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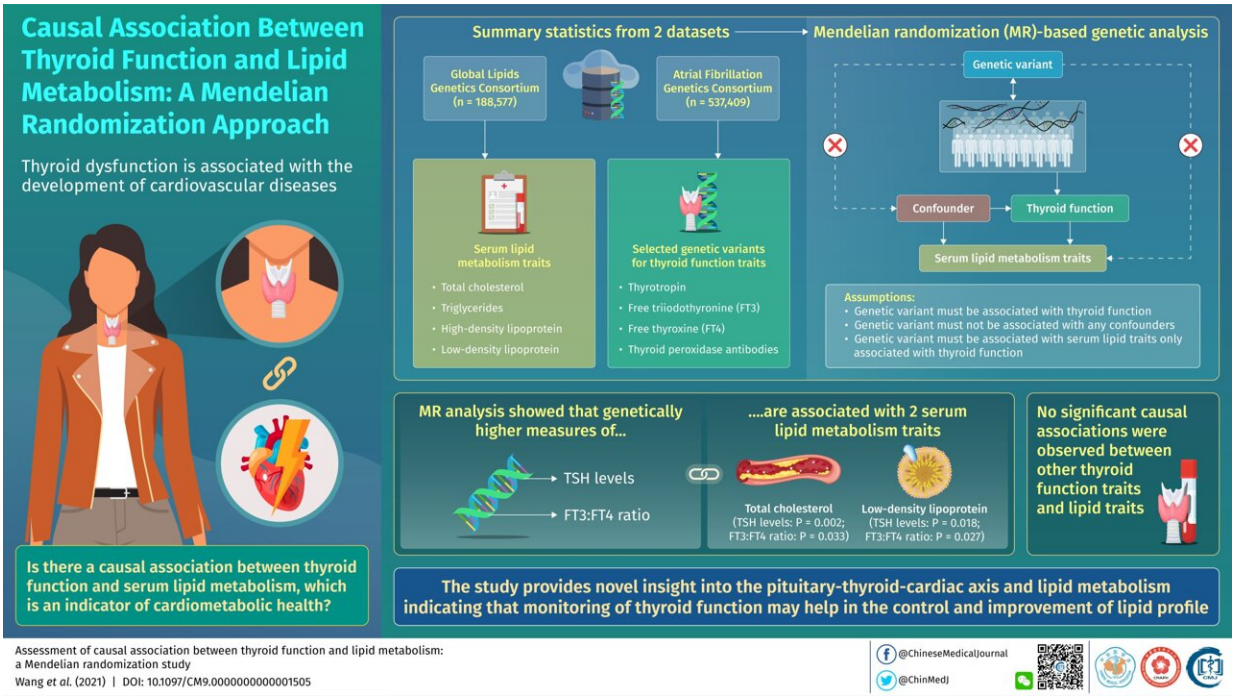

A recent study published in Chinese Medical Journal reveals an association between thyroid function and serum lipid profiles with the help of a genetic analysis technique known as "Mendelian randomization" Credit: Chinese Medical Journal

Thyroid hormones are amino acid-based molecules produced by the thyroid gland. Involved in direct or indirect regulation of key metabolic pathways, these molecules play critical roles in the development and

normal functioning of the body. The mechanism of how thyroid hormones exert their effect on each other as well as on other metabolic pathways is complex, but a two-way feedback loop is central to their biological activity. Dysregulation of the feedback loop that controls their production affects other biochemical pathways, causing various ailments including those related to the cardiovascular system, liver function, or bone development.

Several clinical studies have shown the effect of thyroid hormones on lipid levels: That treating the patients with thyroid hormone analogs helps to improve their lipid level, for example, or that thyroid hormones are associated with glycolipid metabolism and increased risk of cardiovascular diseases (CVD). These results highlight the possibilities of predicting the risk of lipid-related diseases or designing a CVD treatment strategy based on thyroid hormones. But such efforts would require the base of a biological cause-and-effect relationship between thyroid hormones and lipid profile, an association that has remained unproven thus far.

It is notable that the results of the previously conducted clinical studies, however intriguing, have remained unable to pinpoint thyroid hormones as the probable cause of change in the lipid profile. This is because many confounding factors might have impacted both, blurring the cause-and-effect relationship between thyroid function and lipid profiles. Additionally, the observed relationship between the two could reflect reverse causation, where the change in lipid profile affected the thyroid function. Thus, to leverage the observed association between thyroid function and serum lipid profile for designing treatment strategies for lipid-related diseases, a better understanding of their causal dynamics becomes imperative.

Now, a team of researchers led by Dr. Yi-Da Tang, Department of Cardiology, Peking University, in their recently published article in

Chinese Medical Journal, have presented a scientific basis for identifying thyroid function as a causal factor capable of affecting the serum lipid levels. The team genetically analyzed epidemiology data using a method called Mendelian randomization (MR). MR is based on the assumption that genetic alleles are randomly assorted in the population and act as proxies for environmental exposures that alter the biological disease risk in a manner that is less likely to be impacted by behavioral, social, or physiological confounding factors. Dr. Tang, who is also the corresponding author of the study, explains, "As we tried to decipher the association between thyroid function and lipid profile, MR offered a solution to mimic a perfectly-designed randomized control trial. The approach allowed us to ward off the confounding factors and the chance of reverse causation, and let us observe whether there exists a hidden causal effect of thyroid function on lipid-related disease."

In their study, the researchers analyzed the genotype data of thousands of people from two genome-wide-association-studies (GWAS) datasets. For clinical measures of thyroid function, they considered levels of thyrotropin (TSH), free thyroxine (FT4), ratio of free triiodothyronine (FT3) and FT4 (FT3:FT4), and thyroid peroxidase antibodies (TPOAb) as essential thyroid traits known to be related with various disease conditions. Then from the GWASs, they identified 115 single-nucleotide polymorphisms that represented the genetic variants for the thyroid function traits. Using MR analysis, the researchers assessed the effect of each of the selected genetic variants for thyroid function on the selected lipid metabolism traits at the population level. They found that as potential causal factors for altered lipid levels, the genetically altered levels of two of the selected thyroid traits, TSH level and FT3:FT4 ratio, were related to the elevated levels of TC and LDL of the individuals. However, the genetically predicted FT4 level and TPOAb concentration were not associated with any of the serum lipid traits.

The team's findings establish a distinct association between thyroid

function and serum lipid metabolism. Interpreting the clinical significance of their result, Prof. Tang concludes, "Our study highlights the importance of pituitary-thyroid-cardiac axis in diseases related to dyslipidemia. As we have proved the causal association, patients with thyroid diseases or those on thyroid replacement therapy should pay attention to the thyroid trait and serum lipid profiles to prevent the development of cardiometabolic diseases."

More information: Jing-Jia Wang et al, Assessment of causal association between thyroid function and lipid metabolism: a Mendelian randomization study, *Chinese Medical Journal* (2021). DOI: 10.1097/cm9.0000000000001505

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