Study reveals link between transthyretin levels and heart disease risk

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Cumulative incidence of heart failure stratified by transthyretin levels. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-50231-1

Physician–scientists from the University of Alabama at Birmingham Marnix E. Heersink School of Medicine have uncovered significant
findings regarding the impact of transthyretin, or TTR, protein levels on heart disease risk.

The study, recently published in *Nature Communications*, explores how variations in TTR levels are associated with adverse clinical outcomes, providing new insights into the prevention and management of amyloid heart disease.

Transthyretin is a transport protein produced in the liver, and its misfolding is linked to the development of cardiac amyloidosis, a condition that leads to *heart failure* and increased mortality.

The study, led by Pankaj Arora, M.D., and Naman Shetty, M.D., examined data from 35,206 participants in the UK Biobank. The researchers investigated the clinical correlates of TTR levels, differences in TTR levels based on genetic variations and the association of TTR levels with health outcomes.

Arora and his team found that lower TTR levels are significantly associated with an increased risk of heart failure and all-cause mortality. Specifically, individuals with low TTR levels had a 17% higher risk of heart failure and an 18% higher risk of death from any cause compared to those with higher TTR levels. These findings were even more pronounced in individuals carrying the V142I TTR gene variant, which is known to destabilize the TTR protein.

The study revealed that TTR levels were lower in females compared to males and were influenced by several health factors. Higher systolic and *diastolic blood pressure*, total cholesterol, albumin levels, triglyceride levels, and creatinine levels were associated with increased TTR levels.

Higher C-reactive *protein levels* were linked to lower TTR levels. Notably, carriers of the V142I TTR gene variant had significantly lower
TTR levels compared to non-carriers, highlighting a genetic influence on this protein.

"Our research highlights the critical role of TTR levels in predicting heart disease risk," Arora said. "By understanding the factors that influence TTR levels, we can better identify individuals at high risk and develop targeted interventions to prevent adverse outcomes."

"These findings underscore the potential benefits of incorporating TTR level measurements in screening programs, especially for individuals with genetic predispositions," Shetty said.

Arora, the senior author and a cardiologist at the UAB Cardiovascular Institute, says the implications of this study are far-reaching. It suggests that monitoring of TTR levels could be a valuable tool in managing heart disease risk, particularly for those with known genetic variations like the V142I TTR variant. Low TTR levels raise the pre-test probability of a positive genetic test, specifically for detecting the V142I variant, which typically takes time to process.

"This information can be used to counsel family members while they await the results of genetic testing," Arora said. "This research marks a significant step forward in the quest to understand and mitigate the risks associated with cardiac amyloidosis and other heart-related conditions."

**More information:** Naman S. Shetty et al, Determinants of transthyretin levels and their association with adverse clinical outcomes among UK Biobank participants, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-50231-1](https://doi.org/10.1038/s41467-024-50231-1)
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