

## **Resting heart rate and type 2 diabetes: A complex relationship in need of greater understanding**

Patricia B Munroe PhD<sup>1,2</sup>, Julia Ramirez PhD<sup>1,3</sup> and Stefan van Duijvenboden PhD<sup>1,3</sup>

1. Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom
2. National Institutes of Health Research Barts Cardiovascular Biomedical Research Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom
3. Institute of Cardiovascular Science, University College London, London, United Kingdom

**Brief title:** heart rate and type 2 diabetes, a complex relationship

**Corresponding author:** Professor Patricia B. Munroe, Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ, United Kingdom Email: [p.b.munroe@qmul.ac.uk](mailto:p.b.munroe@qmul.ac.uk),  
Twitter: @munroe\_patsy

### **Conflict/disclosure statement**

All authors have no conflicts or disclosures

Numerous epidemiological studies have consistently linked elevated resting heart rate (RHR) with increased risk of cardiovascular disease and all-cause mortality in men and women. A 10 beats/min (bpm) increase in RHR is associated with a 6 to 18% increased risk for coronary artery disease (CAD), sudden cardiac death, heart failure, stroke and all-cause mortality (1,2) and clinical trials have shown that lowering RHR reduces cardiovascular risk (3). Additionally, higher RHR has been associated with an increased likelihood of developing type 2 diabetes (T2D). For example, participants in the highest (> 72.7 bpm) versus lowest RHR quartile (< 60.1 bpm) had a 60% increased risk of developing T2D over a 9 year follow-up period in the Atherosclerosis Risk in Communities study (4). However, these findings are not always consistent as some studies have subsequently reported the association is attenuated when body mass index (BMI) and fasting glucose levels are accounted for (5).

Epidemiological studies report associations between RHR and T2D, they do not inform on causal relationships and shared biology, which is crucial to understand underlying common mechanisms. A high RHR has been linked to increased sympathetic activity, insulin resistance and the development of T2D (6). However, the development of T2D may lead to metabolic sequelae that increase RHR, providing an alternative explanation of the observed associations (7).

In this issue, Guo et al. (8) present a study that investigates the genetic correlation of RHR with T2D and eight cardiometabolic traits (fasting insulin, fasting glucose, triglycerides, waist-hip-ratio [WHR], BMI, LDL, TC and HDL) and assesses causal relationships and shared biological mechanisms. The investigators firstly performed a genome-wide association study for RHR in

the UK Biobank, and assessed genetic correlations using publicly available GWAS summary statistics for T2D and the cardiometabolic traits (9). They found 437 independent loci for RHR, 327 of which were novel. They found RHR was genetically correlated to T2D ( $r_g = 0.22$ ,  $P = 2 \times 10^{-22}$ ) and with varying degrees to 6 of the cardiometabolic traits studied (fasting insulin, fasting glucose, WHR, BMI and triglycerides) with a negative correlation with HDL. The observed correlations were relatively modest, but some were of a similar magnitude to those reported for LDL and CAD ( $r_g = 0.25$ ) (9). To interrogate potential causal relationships they used bi-directional mendelian randomization (MR) using generalized summary data (10). This analysis indicated RHR was causally related with increased T2D risk and vice versa: Exposure to a 10 bpm increase in RHR was found to be causally related with a 1.12 fold risk of T2D, which is similar to the 1.17 fold risk reported in observational studies. Conversely, the estimated causal effect of T2D on RHR was 0.32 bpm, corresponding to per doubling increment in T2D prevalence. Causal associations were also observed between RHR and both BMI and WHR in both directions. Using results from the newly identified RHR loci and published T2D loci, the authors explored if there were any genes whose expression is related to RHR and T2D/cardiometabolic traits using a transcriptome-wide association study (TWAS) and if any of the genes were common to both traits. A TWAS is a statistical test that leverages expression datasets to identify genes whose expression is correlated with a trait of interest. Several genes and tissues were highlighted for RHR, providing new information on potential candidate genes and biology of RHR. There were 135 TWAS genes shared between RHR and T2D/cardiometabolic traits in tissues from the nervous cardiovascular and immune systems, providing candidate genes and systems for follow up work.

A primary observation from this study was the causal associations reported for RHR and T2D and vice versa, with the stronger causal association being from RHR to T2D. Interpreting MR results, which indicate causality in both directions is challenging, and there are limited studies in the literature reporting such findings (11). The authors used GSMR, this method utilises variants which are strongly associated with the risk factor and it has additional methods you can use to account for pleiotropic variants and conditional analyses. It is not clear in the paper by Guo et al what genetic variants were used for the MR analyses for either RHR or T2D/cardiometabolic traits and how much variance did these genetic variants explain. Further checks on heterogeneity should be done (for example, MR-PRESSO or MR Steiger) and the bidirectional MR findings should be validated in independent datasets (11). Gene-exposure interactions could also be studied, as physical activity is associated with RHR (12). These additional results would provide robust underpinnings for the reported observations and would discern the strength and directions of the causal relationships.

With the discovery of 327 novel loci for RHR, the authors interrogated this dataset for candidate genes for RHR and identified shared genes whose expression was associated with RHR and T2D/ related cardiometabolic traits. Studying the overlap in gene expression across traits may implicate altering the levels of proteins regulating both RHR and cardiometabolic traits, which may provide useful insights into the shared etiology between them. As commented by the authors, there were relatively smaller sample sizes for metabolic traits in reference panels for certain tissues and this may lead to reduction in power to detect signals with small to moderate effects. Most of the shared genes between RHR and T2D were observed in nervous tissue, and

cardiovascular and immune systems. The results indicated genes involved in glucose homeostasis, energy metabolism, and autonomic nervous activity. One of the candidate genes revealed by TWAS was *GCKR*, which encodes a regulatory protein that inhibits glucokinase in liver and pancreatic islet cells and is known to play an important role in the glucose homeostasis. Although the authors do not comment on its involvement in modulating RHR, it may be that changes in glucose homeostasis also affect cardiac energy homeostasis and metabolic properties, which translate into changes in RHR. Previous studies have suggested several biological mechanisms by which sympathetic activation may predispose to T2D. Findings of overlapping genes in nervous tissue provide some support for these hypotheses. For example, sympathetic activation may inhibit insulin secretion from pancreatic  $\beta$  cells and activation of the renin-angiotensin-aldosterone system, which increases RHR and leads to insulin resistance. Further work will be needed to delve deeper into autonomic mechanisms, like using more specific expression data from nervous tissues. This is especially important, as our current understanding regarding RHR and T2D indicates a vicious cycle in causal relations, as relatively high RHR is often found together with increased blood pressure, atherogenic blood lipid profile, inflammation, obesity, and metabolic syndrome in which elevated RHR and cardiometabolic risk factors and high blood pressure may be intermediate accelerators of the vicious cycle.

The work presented in this issue can be viewed as a very first step in untangling the causal relationship between RHR, T2D and cardiometabolic disorders. The results further underline the complexity of this relationship. The bi-directional causality especially raises questions and further validation will be necessary before beginning to address any clinical implications of the

work. As the authors state in their limitations, the possibility that RHR is mediating the effect or other latent factors on T2D cannot be ruled out. Functional studies on the shared genes may be useful in guiding this process. The promise of potential drug intervention to lower RHR based on MR results is alluring, however the life-long exposure (MR evidence) may not translate to short-to medium-term intervention from pharmacological therapy in reducing T2D risk.

## References

1. Aune D, Sen A, ó'Hartaigh B et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality – A systematic review and dose–response meta-analysis of prospective studies. *Nutrition, Metabolism and Cardiovascular Diseases* 2017;27:504-517.
2. Zhang D, Wang W, Li F. Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. *Canadian Medical Association Journal* 2016;188:E384-E392.
3. Ferrari R, Fox K. Heart rate reduction in coronary artery disease and heart failure. *Nat Rev Cardiol* 2016;13:493-501.
4. Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study, 1987-1998. *Circulation* 2003;107:2190-5.
5. Carnethon MR, Yan L, Greenland P et al. Resting heart rate in middle age and diabetes development in older age. *Diabetes Care* 2008;31:335-9.

6. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008;51:1725-33.
7. !!! INVALID CITATION !!! (6).
8. Yanjun Guo, Wonil Chung, Zhaozhong Zhu et al. Genome-wide assessment for RHR and shared genetics with T2D and cardiometabolic traits in UK Biobank. *Journal of the American College of Cardiology* 2019;XXX.
9. Bulik-Sullivan B, Finucane HK, Anttila V et al. An atlas of genetic correlations across human diseases and traits. *Nature Genetics* 2015;47:1236.
10. Zhu Z, Zheng Z, Zhang F et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nature Communications* 2018;9:224.
11. Xu S, Gilliland FD, Conti DV. Elucidation of causal direction between asthma and obesity: a bi-directional Mendelian randomization study. *Int J Epidemiol* 2019.
12. Zheng J, Baird D, Borges MC et al. Recent Developments in Mendelian Randomization Studies. *Curr Epidemiol Rep* 2017;4:330-345.