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Title

Nocturnal Respiratory Rate: a Stable, Heritable Trait that Predicts All-Cause Mortality

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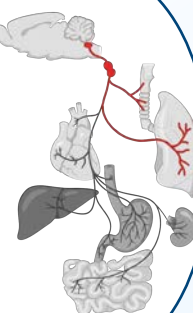
et al.

Publication Date

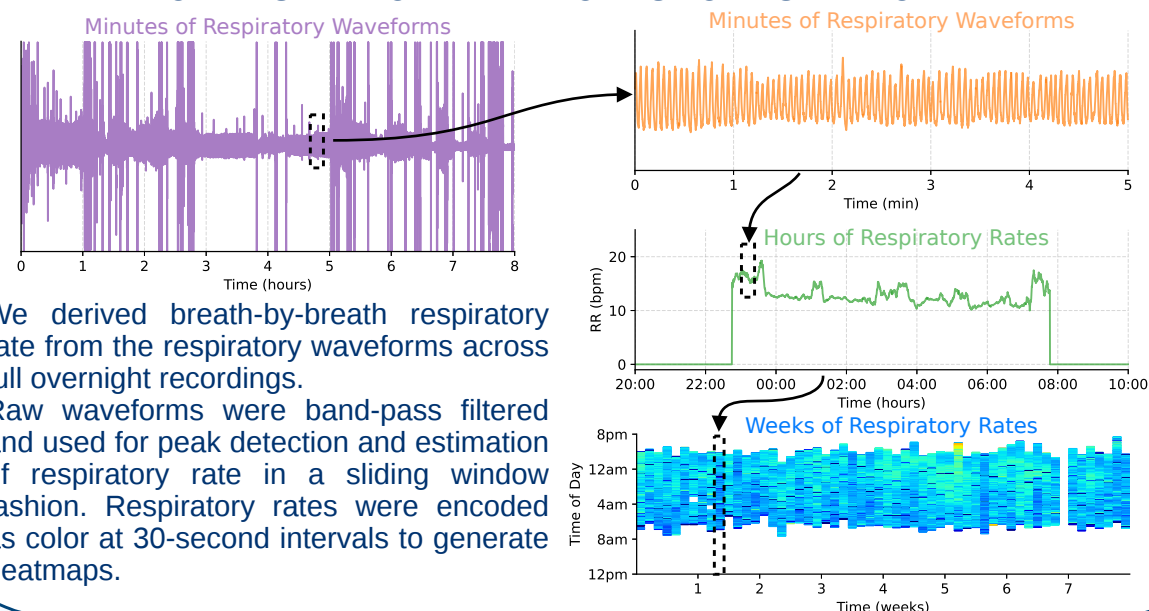
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INTRODUCTION

- Respiratory rate is a fundamental vital sign. It is controlled by a site in the brain that integrates inputs from throughout the body. However, its determinants and prognostic potential are undefined.
- During sleep, it can be passively and longitudinally monitored to improve measurement quality while avoiding confounding by activity or conscious inputs.
- We performed longitudinal respiratory monitoring and analyzed paired polysomnography (PSG) and genotyping data from large cross-sectional observational cohorts. We asked whether nocturnal respiratory rate (NRR) is (i) reliably measurable, (ii) prognostic for mortality, and (iii) shaped by common genetic variation (inherited).



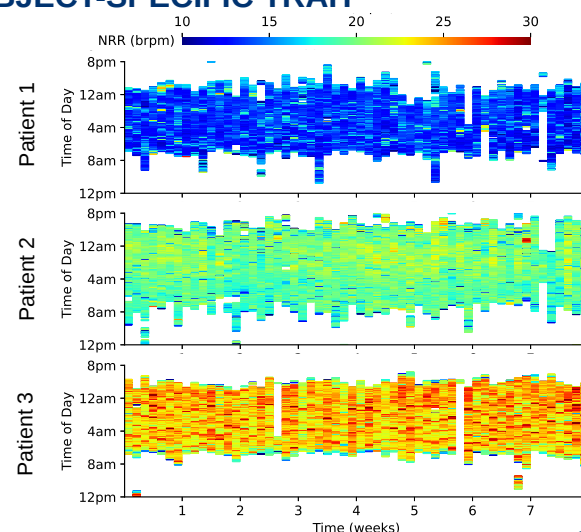
FROM RESPIRATORY WAVEFORMS TO RESPIRATORY RATE



NRR IS A STABLE, SUBJECT-SPECIFIC TRAIT

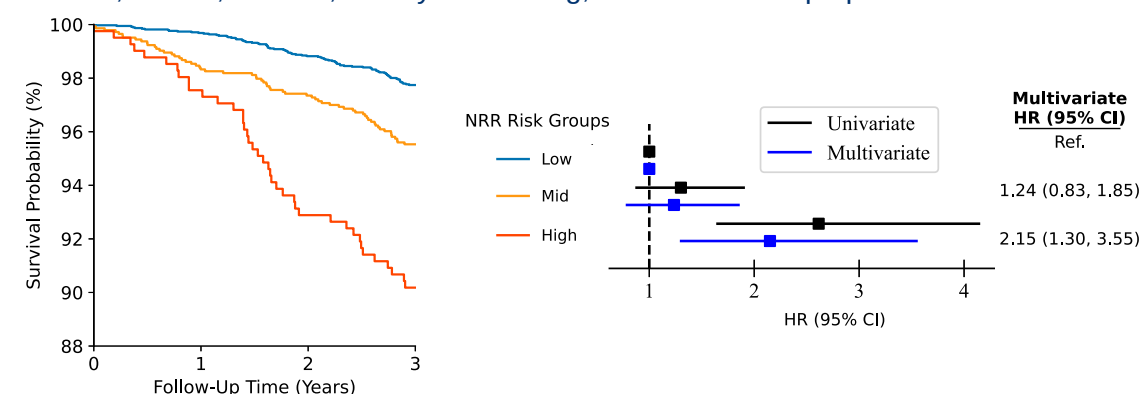
Using non-contact home bed sensors, we compared nocturnal respiratory rates of multiple patients across time:

- For each individual, NRR was highly consistent within nights and between nights.
- Between individuals, baseline NRR varied substantially.
- This suggests median NRR is a patient-specific biomarker.
- The determinants of this patient-specific NRR set-point and its clinical significance are unknown.



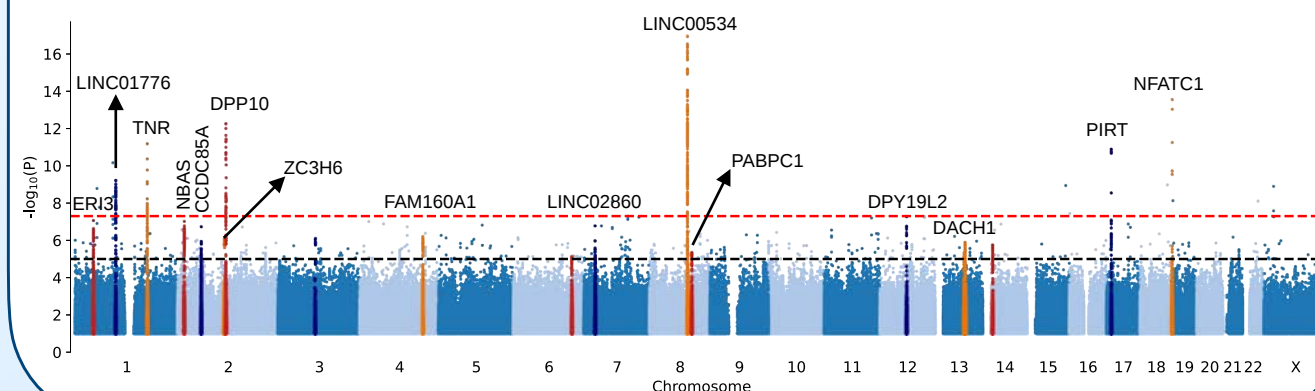
NRR PREDICTS ALL-CAUSE MORTALITY

- We performed a survival analysis in 5,679 older adults from the Sleep Heart Health Study (SHHS).
- Individuals in the high NRR risk group exhibit a nearly 5-fold higher mortality as well as a significantly higher hazard ratio for all-cause mortality: HR 2.15 (95% CI 1.30–3.55).
- Models are adjusted for: age, gender, obesity, heart failure, atrial fibrillation, diabetes and hypertension, COPD, asthma, history of smoking, and severe sleep apnea.



THE FIRST GWAS FOR NOCTURNAL RESPIRATORY RATE

- To determine if NRR has identifiable genetic determinants, we combined PSGs from NSRR with genotyping data from dbGaP from SHHS, HCHS/SOL, MESA, and CFS studies to perform the first GWAS analysis of respiratory rate (N=14,277).
- Genome-wide significant loci implicated genes spanning a range of biological functions, including ion-channel (DPP10), neuronal (PIRT), developmental and structural (TNR and DACH1), and immune- and cardiac-relevant (NFATC1) genes.
- SNP-based heritability was estimated to be $h^2_{\text{SNP}} = 0.247$ (SE 0.035).



CONCLUSIONS

Nocturnal Respiratory Rate (NRR) is a patient-specific biomarker that can be longitudinally monitored and cross-sectionally studied using overnight sleep studies (PSGs). The determinants of NRR set points are largely unknown, but they are heritable and predict mortality with GWAS significant loci near genes plausibly linked to respiratory and autonomic control. Together, these results suggest NRR is a prognostic biomarker with inherited and acquired determinants.

ACKNOWLEDGEMENTS

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- N. Harrington; et al. "Nocturnal Respiratory Rate Dynamics Enable Early Recognition of Impending Hospitalizations". In: medRxiv (Mar. 2022). doi: 10.1101/2022.03.10.22272238.