Impact of measurement noise in cardiac imaging on genome-wide association studies

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BACKGROUND

- Recent studies have leveraged quantitative traits from imaging to amplify the power of genome-wide association studies (GWAS) and gain further insights into the biology of diseases and traits.
- The standard approach to enhance GWAS power is by augmenting the cohort size, yet this can often prove to be expensive or unattainable.
- However, measurement error and noise are intrinsic to phenotyping and can impact downstream genetic analyses. **To what extent can we boost the GWAS power by improving the precision of phenotyping?**

METHODS

- We conducted a GWAS of 22,859 subjects in the UK Biobank with cardiac MRI imaging for genetic associations with **left ventricular ejection fraction** (LVEF), an important but noisy measurement.
- To analyze the impact of imaging measurement noise, we added varying amounts of noise to LVEF measurements and inspected corresponding GWAS results.
- To quantify the loss in power, we assessed the number of loci that persisted after adding noise and compared it with a drop in sample size.

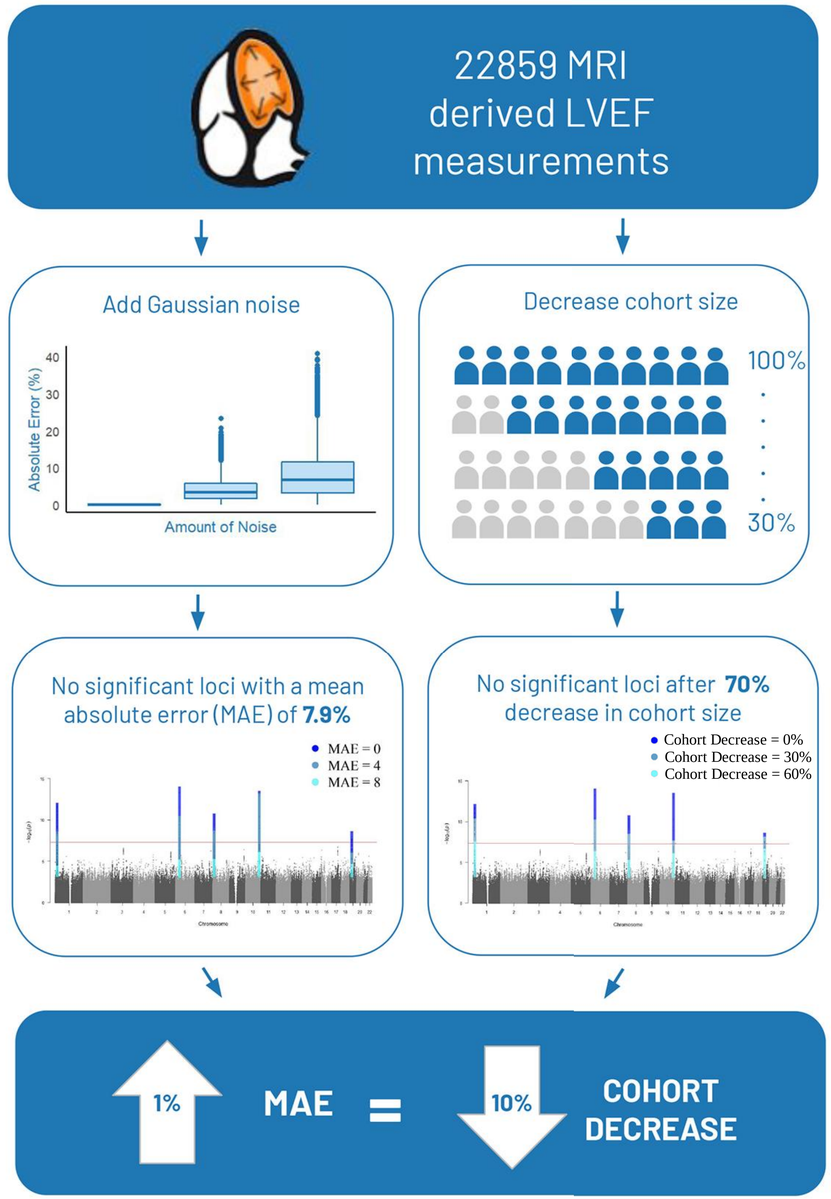
RESULTS

- Introducing 7.9% of measurement noise can eliminate all genetic associations in an LVEF GWAS with almost forty thousand individuals.
- An increase of **1% in mean absolute error (MAE) in LVEF had an equivalent impact on GWAS power as a decrease of 10% in the cohort sample size.**
- Two different methods of measuring LVEF from MRI resulted in different GWAS power. Namely, the deep learning method identified 7 significant loci, while the InlineVF method identified 5.

CONCLUSION

- Measurement error in quantitative cardiac phenotypes significantly impacts the results of downstream genetic analyses
- Efforts to **improve phenotypic precision** are **important for improving power in GWAS** and could have particular benefit when the same size is limited.

Optimizing **phenotyping precision** is a cost-effective way to improve **the discovery of genetic associations**



DISCUSSION

- This degree of sensitivity to phenotype imprecision could explain the difference in findings between genetic studies leveraging echocardiography and cardiac MRI-based measurements.
- The relative improvement relationships that we obtained between various facets of cohort design might be beneficial to researchers to understand the cost-benefit of improving the precision vs. increasing the cohort size.

FIGURE 1

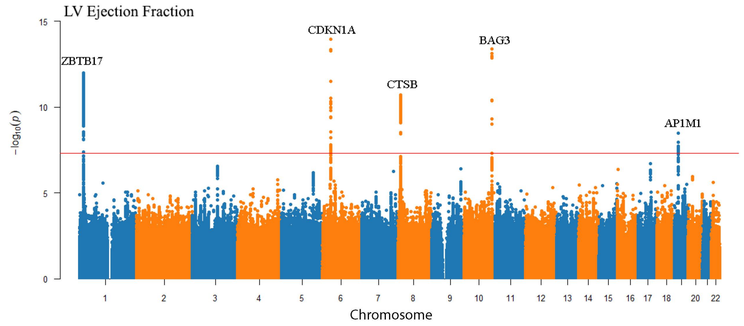


FIGURE 2

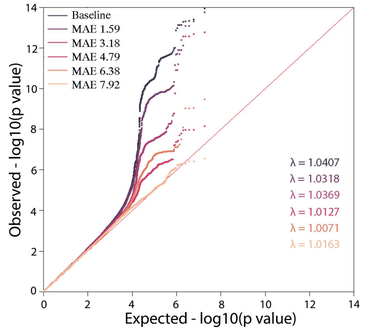


FIGURE 3

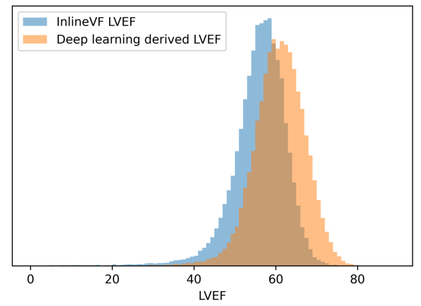
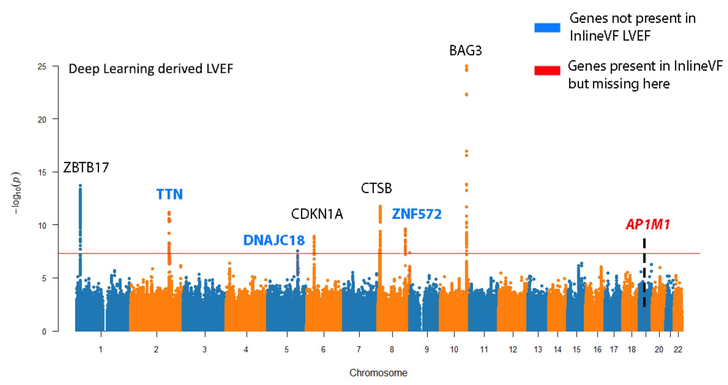


FIGURE 4



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