A polygenic architecture of medication-use across medical conditions

Rohde, Palle Duun; Nyegaard, Mette

A polygenic architecture of medication-use across medical conditions

Palle Duun Rohde[1*] & Mette Nyegaard[2]

[1] Department of Chemistry and Bioscience, Aalborg University, Denmark; [2] Department of Biomedicine, Aarhus University, Denmark

*palledr@bio.aau.dk

Research aim

To investigate the genetic architecture and biological mechanisms underlying medication-use in the general population.

Previously, Wu et al (2019) performed a genetic analysis in the UK Biobank on medication-use of 23 medication categories.

Here, we extend on these results by investigating medication-use, defined as the total number of different medications currently being used. We do this by performing a GWAS, heritability estimates and genetic correlation analysis.

Conclusion

We have shown that the total number of different medications people in the UK Biobank currently use has a polygenic architecture.

We identified 57 independent quantitative trait loci for medication-use, and showed that 14% of the phenotypic variation was explained by common genetic variants.

Medication-use had positive genetic correlation with heart diseases, and was negatively correlated with parents age of death and years in school.

The genetic architecture of medication-use is complex, and is not solely driven by common diseases, as indicated by the strong negative genetic correlation.

ORCID

No conflict of interest to declare

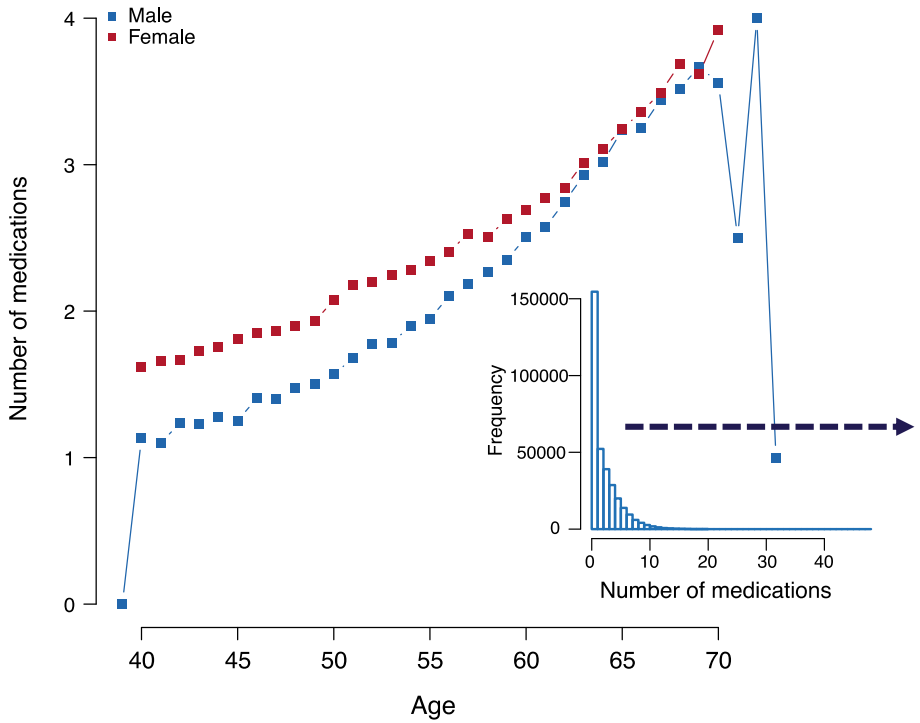
DATA & METHODS

AALBORG UNIVERSITY
DENMARK

Medication-use

From the UK Biobank we extracted information on medication-use from *n*=335.744 unrelate white-British individuals (approval ID 31269)

Medication-use was defined as the total number of different medications currently being used by the participants.



Genetic analysis of medication-use

For the genetic analyses we used ~9 million imputed common genetic variants.

We performed the following analyses:

- Genome-wide association study (by PLINK [REF])
- Genetic correlations (by LD Hub [REF])
- Heritability estimation and partitioning (by SumHer [REF])
- Generic scores (by R-qgg [REF])

3,337 different medications are currently being used.

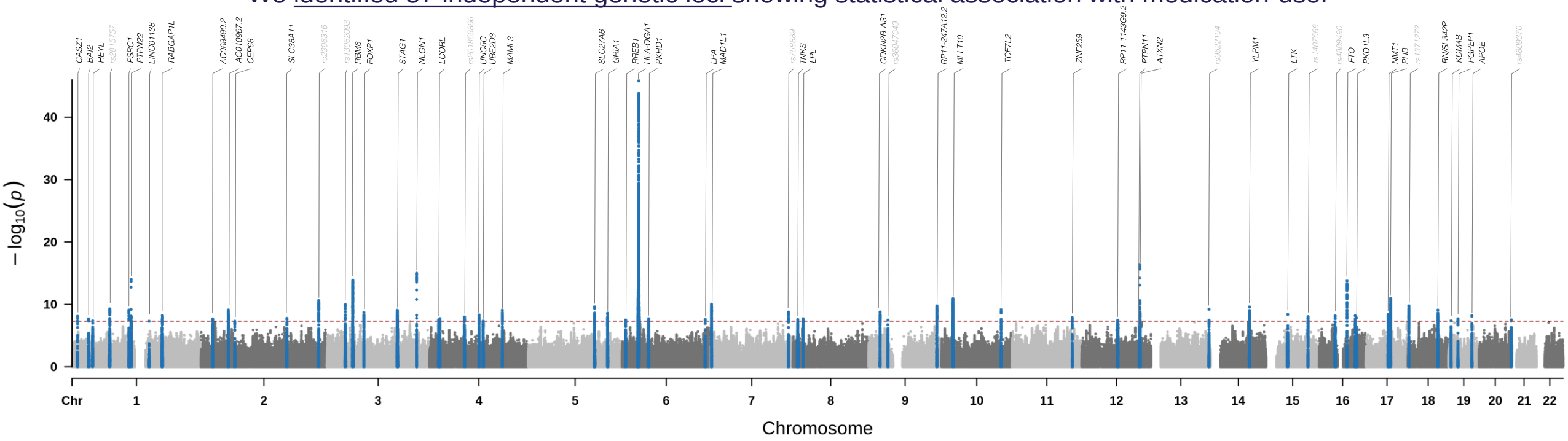
Top-used drugs (used by 18,000-66,000 individuals) are for;

- heart failure and hypertension (ramipril, bendroflumethiazide)
- lowering colesterol (simvastatin)
- stomach ulcer (omeprazole)
- painkillers and fever lowering (aspirin, ibuprofen, paracetamol)

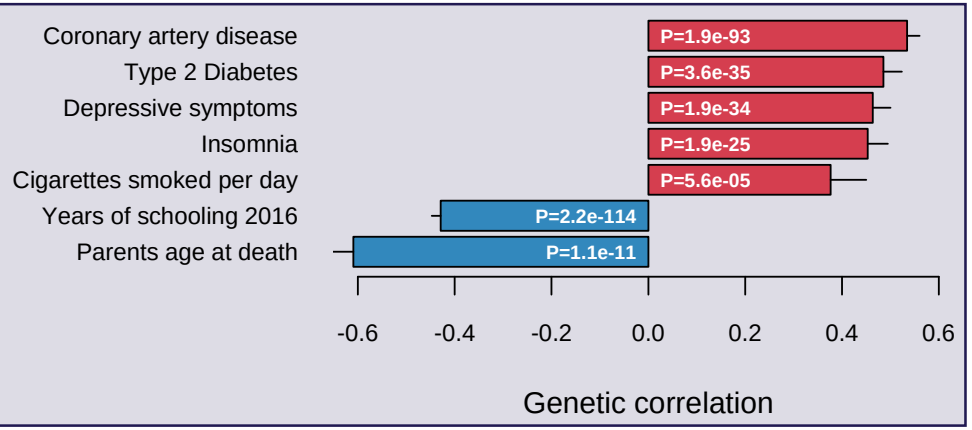
RESULTS-I

AALBORG UNIVERSITY
DENMARK

We identified 57 independent genetic loci showing statistical association with medication-use.



Estimated genetic correlations showed that medication-use was positively correlated with common diseases, smoking and depressive symptoms; and was negatively correlated with years in school and age of parents death.

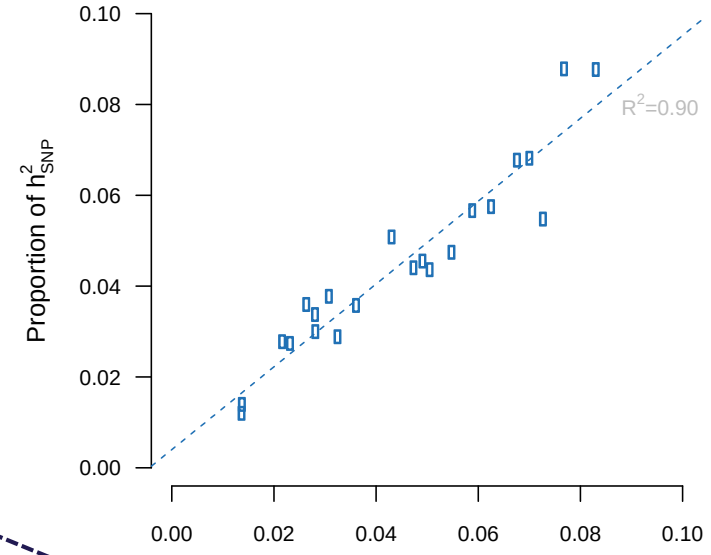


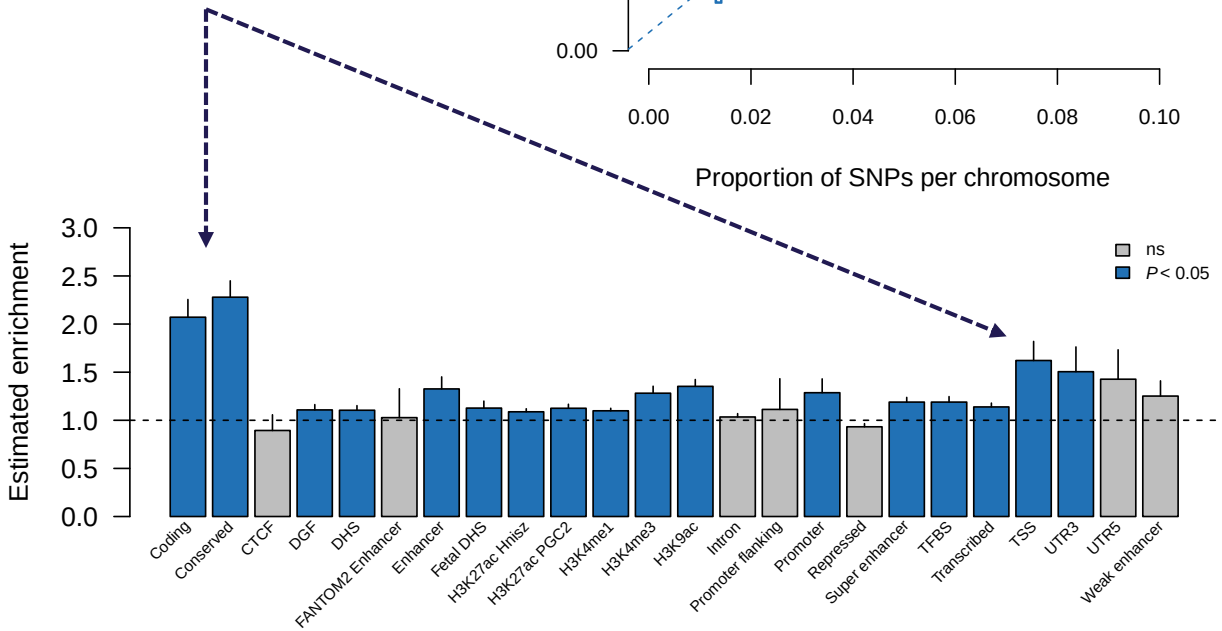
RESULTS-II

AALBORG UNIVERSITY
DENMARK

Decomposing heritability

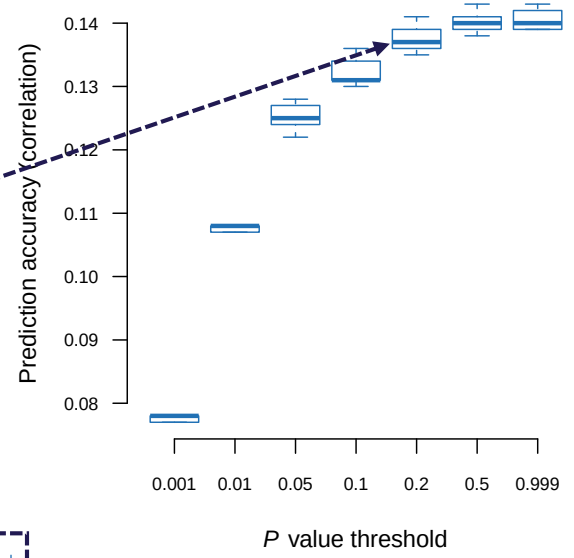
The heritability of medication-use was estimated to 0.14, with equal contribution from each autosomal chromosomes, with some genomic regions highly enriched.

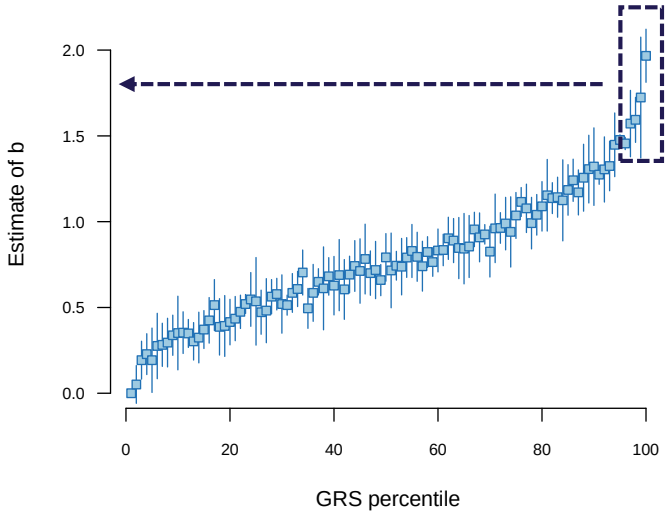




Predicting medication-use

After applying linkage disequilibrium pruning of the genetic variants (r^2<0.7) the maximum prediction accuracy was obtained when including genetic markers with *P*-values < 0.2 (by five-fold cross validation).





Dividing participants into percentiles according to their genertic scores, and estimate their effect size on medication-use, the 5% with highest genetic load, used on average 1.8 more drugs than the bottom distribution.

CONCLUSION

AALBORG UNIVERSITY
DENMARK

Study summary

Findings from this study;

… 57 independent quantitative trait loci for medication-use.

… 14% of the total variation in medication-use in UKBB is explained by common genetic variants.

… coding and conserved regions are heavily enriched by genetic variation for medication-use.

… positive genetic correlation with heart disease, diabetes, depression, insomnia and smoking.

….negative genetic correlated with parents age of death and years in school.

… mean prediction accuracy of medication-use was 0.14.

… individuals with top 5% genetic load used ~1.8 more drugs than the bottom distribution.

Perspective

Our results demonstrate that medication-use *per se* is a complex trait irrespectively of medical condition.

The finding that current medication-use was strongly correlated with smoking behaviour, parents age of death, educational level and insomnia, suggest that the genetic architecture of medication-use is not biased towards major common diseases.

Understanding the genetic aetiology of complex diseases has been suggested as the route for improving medical treatment. However, when current medication-use, across medical conditions, appears to have a polygenic architecture, it might be inadequate to solely rely on analyses of complex diseases for improving medical treatment.

Thus, medication-use, or better medication response, is likely to be yet another puzzle piece in understanding complex human diseases, and for providing better medical treatment for future generations.

LUNDBECKFONDEN

Grant number: R287-2018-735

ORCID

No conflict of interest to declare