TITLE: Evaluation of Polygenic Prediction Methodology within a Reference-Standardized Framework

FULL AUTHOR LIST: Oliver Pain\textsuperscript{1,2}, Kylie P. Glanville\textsuperscript{1}, Saskia Hagenaars\textsuperscript{1}, Saskia Selzam\textsuperscript{1}, Anna E. Fürtjes\textsuperscript{1}, Helena Gaspar\textsuperscript{1}, Jonathan R. I. Coleman\textsuperscript{1}, Kaili Rimfeld\textsuperscript{1}, Gerome Breen\textsuperscript{1,2}, Robert Plomin\textsuperscript{1}, Lasse Folkersen\textsuperscript{2}, Cathryn M. Lewis\textsuperscript{1,2,3}.

AFFILIATIONS:
\textsuperscript{1}Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, SE5 8AF, United Kingdom
\textsuperscript{2}NIHR Maudsley Biomedical Research Centre, South London and Maudsley NHS Trust, London, SE5 8AF, UK.
\textsuperscript{3}Institute of Biological Psychiatry, Sankt Hans Hospital, Copenhagen, 4000 Roskilde, Denmark
\textsuperscript{4}Department of Medical and Molecular Genetics, Faculty of Life Sciences and Medicine, King’s College London, London, SE1 9RT, UK.

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ABSTRACT:

\textbf{Background:} The predictive utility of polygenic scores is increasing but it is unclear which polygenic scoring method performs best. It is often advantageous to calculate polygenic scores using a reference-standardized framework, using a common set of variants and reference-estimated linkage disequilibrium and allele frequencies. This study evaluates the predictive utility of several polygenic scoring methods within a reference-standardized framework.

\textbf{Methods:} The following methods are evaluated using anthropometric, neuropsychiatric
and complex disease outcomes measured in UK Biobank and Twins Early Development Study (TEDS): p-value thresholding and clumping (pT+clump), SBLUP, lassosum, LDPred, PRScs and SBayesR. Strategies to identify optimal p-value threshold and shrinkage parameters are compared, including 10-fold cross validation, pseudovalidation (no validation sample), and multi-polygenic score elastic net models.

**Results**: Using 10-fold cross-validation to identify the most predictive p-value threshold or shrinkage parameter, lassosum, PRScs and LDPred provided optimal prediction (relative improvement of 14-17% over pT+clump). Using pseudovalidation to optimize the polygenic score, the best method was PRScs, with a relative improvement of >11% over other pseudovalidation methods (lassosum, SLBLUP, SBayesR, LDPred), and only 1% worse than the best polygenic score identified by 10-fold cross validation. Elastic net models containing polygenic scores based on a range of parameters consistently improve prediction over any single polygenic score.

**Conclusion**: Within a reference-standardized framework, the best polygenic prediction was achieved using lassosum, PRScs, modelling multiple polygenic scores that are derived using a range of parameters. As polygenic scores are widely applied in research studies, users should be aware of differences in prediction across methods.

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