Genetics and population analysis

RápidoPGS: a rapid polygenic score calculator for summary GWAS data without a test dataset

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Abstract

Motivation: Polygenic scores (PGS) aim to genetically predict complex traits at an individual level. PGS are typically trained on genome-wide association summary statistics and require an independent test dataset to tune parameters. More recent methods allow parameters to be tuned on the training data, removing the need for independent test data, but approaches are computationally intensive. Based on fine-mapping principles, we present RápidoPGS, a flexible and fast method to compute PGS requiring summary-level Genome-wide association studies (GWAS) datasets only, with little computational requirements and no test data required for parameter tuning.

Results: We show that RápidoPGS performs slightly less well than two out of three other widely used PGS methods (LDpred2, PRScs and SBayesR) for case–control datasets, with median $R^2$ difference: -0.0092, -0.0042 and 0.0064, respectively, but up to 17 000-fold faster with reduced computational requirements. RápidoPGS is implemented in R and can work with user-supplied summary statistics or download them from the GWAS catalog.

Availability and implementation: Our method is available with a GPL license as an R package from CRAN and GitHub.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Genome-wide association studies (GWAS) have been widely successful at identifying a large number of genetic variants (usually single nucleotide polymorphisms, or SNPs) associated with a wide range of diseases and complex traits (Buniello et al., 2019). Most genetic variants have a small individual effect on the tested traits and thus have low predictive power (Dudbridge, 2013; International Schizophrenia Consortium et al., 2009; Yang et al., 2010). However, simultaneously evaluating the effects of all common SNPs has the potential to explain much of the heritability for complex diseases and phenotypes (Bulik-Sullivan et al., 2015; Yang et al., 2010).

Polygenic scores (PGS) estimate individual propensity to a phenotype (e.g. disease) by summing an individual’s genotypes (coded 0, 1, 2), weighted by their effect sizes, estimated from GWAS data

$$
\sum_{i=1}^{n} \beta_i G_i
$$

where $\beta_i$ is the estimated effect for variant $i$, and $G_i$ the genotype. Challenges relate to the nature of GWAS data to determine the set of SNPs $S$ to use. If ignored, linkage disequilibrium (LD) between variants would mean double-counting the effects of causal variants in high LD with multiple other variants. In addition, error in the estimated effect sizes is most pronounced for small effects, for which true association may not be distinguishable from noise about a null value. Different approaches have been developed to deal with these. Initial approaches selected the most strongly associated variant in each genome wide-significant peak. However, it was soon realized that predictive accuracy could be improved by reducing the significance threshold, to capture more truly associated variants even at the cost of including some false associations (which should add noise, but not bias, to any prediction), especially for highly polygenic diseases (Chatterjee et al., 2016; Dudbridge, 2013). Methods were developed to use an external test set to tune the significance threshold parameter, as well as to use automated LD-pruning algorithms to select independent variants rather than selecting one variant per peak (Euesden et al., 2015; Privé et al., 2019). More statistically sophisticated approaches have since been developed to average over multiple variants in LD without double counting (which is more accurate than selecting just one), shrinking
We created PGS models for eight case–control and two quantitative traits using RápidoPGS and three widely used PGS methods for comparison: LDpred2 (Prive et al., 2020), PRSs (Ge et al., 2019) and SBayesR (Lloyd-Jones et al., 2019).

We then used UK Biobank data as a validation dataset to evaluate the predictive performance of all models and benchmarked their run times.

2 Materials and methods

2.1 Overview of our approach

We compute posterior probabilities of causality at each variant within LD-blocks defined by ldetect (Berisa and Pickrell, 2016) (publically available at https://bitbucket.org/nygcresearch/ldetect-data/src/).

Under a single causal variant assumption, given summary statistics at each SNP, \( \beta_i \) conditionally on it following a normal distribution with specified variance, \( N \) is a normal distribution, and \( W \) is the variance of the prior on the true effect size. We assume that the true causal effect size at any SNP is sampled from an \( N(0, W) \) distribution.

Under the at most one causal variant assumption (often called a single causal variant assumption, but it includes the possibility of no causal variant), the posterior probability that SNP \( i \) is causal in a region of \( n \) SNPs, is

\[
PP_i = \frac{p_i B_F}{p_0 + \sum_{j \neq i} p_j B_F}
\]

where \( p_i \) is the prior SNP \( i \) is causal (typically set to the same value for all SNPs) and \( p_0 = 1 - \sum p_i \) is the prior probability there is no causal variant in the region (Maller et al., 2012). Note therefore \( 0 \leq PP_i < 1 \) and \( \sum PP_i \leq 1 \), so that \( PP_i \) can serve to shrink SNP effect estimates more or less according to the posterior belief that an SNP is causal for a trait.

We set default parameter values for RápidoPGS according to currently widely adopted values: \( p_i = 10^{-4} \), \( W = 0.2^2 \) for case–control traits (Wallace, 2020). There is less consensus on appropriate values of \( W \) for quantitative traits, and we propose to estimate \( W \) given the estimated heritability of the trait under study or a similar trait, which is often available (e.g. at LDHub, http://ldsc.broadinstitute.org/ldhub/, Zheng et al., 2017):

\[
W \approx b^2 / \left( \nu \sum_{i=1}^{\nu} \frac{1}{N_i \sigma_i^2} \right)
\]

where \( b^2 \) is the estimated trait heritability, \( \nu \) is the prior that a given variant is causal (we set \( \nu = 10^{-2} \)), \( p \) is the number of variants, \( N_i \) is the number of individuals used in the inference for variant \( i \) and \( \sigma_i^2 \) is the variance of the estimated effect \( \hat{\beta}_i \) associated with variant \( i \) in the GWAS summary statistics for the trait of choice. See Supplementary Note for the full derivation of the equation.

Alternatively, we can relax the single causal variant assumption. SuSiE (Wang et al., 2020) is an approach for variable selection in regression, based on previous models for Bayesian variable selection in regression (BVSR), but with a different structure that allows for a faster and simpler model fitting procedure based on fitting multiple ‘single-effect regression’ models (multiple-regression models with exactly one variable with non-zero regression coefficient), and then constructing the overall effect vector as the sum of the single-effects vectors (hence, sum of single effects model). SuSiE requires the same parameters (\( p_i \) and \( W \)) as the single causal variant approach, although \( W \) may be internally estimated. We call the two approaches to estimating W ‘informed’ or ‘auto’.

We present RápidoPGS, a lightweight and fast (rápido, in Spanish) method to compute PGS based on fine-mapping approaches that only requires a summary statistics dataset, with no need for an independent test dataset to adjust parameters, and that can generate weights for millions of SNPs in only a few seconds or minutes. RápidoPGS works fully in R, requiring few dependencies. A PGS can be quickly constructed from any GWAS summary statistics dataset, or any GWAS PubMed ID if harmonized datasets are available at GWAS catalog.

As with the ‘prune and threshold’ approach, such methods initially required external independent test datasets to tune their parameters, which can present a barrier to practical use. Recently, automated methods have been developed that remove the need for an external test dataset via hierarchical Bayesian models (Ge et al., 2019; Prive et al., 2020), and perform nearly as well as their externally tuned counterparts. However, they require storage and inversion of large LD matrices, which is computationally intensive, and tuning, internally or externally, adds a further layer of iterative computation. Some approaches mitigate this by adding a thinning step, discarding a subset of SNPs to reduce the burden (e.g. LDpred2 recommends restricting SNPs to those in the HapMap3 panel, Prive et al., 2020), but constructing PGS still takes a long time.

Our framework is based on considering PGS construction as a fine-mapping problem. If we knew exactly the causal variants for a trait, an optimal PGS would comprise the estimated effects of just those variants. Fine-mapping methods estimate probabilities that a variant is causal given observed data. So, in the absence of knowing the exact set of true causal variants, a natural PGS might be constructed as above, with \( wi \) set to the probability variant \( i \) is causal—i.e. by replacing the estimated effect size of each SNP by the posterior expectation of its causal effect. Whilst modern PGS methods focus on the accurate estimation of SNP effects in a joint model, the optimal solution to the joint model is also that which puts non-zero effects only on the true causal variants. We note that many of these approaches involve estimating the probability that a specific SNP has a non-zero effect—the estimand itself in fine-mapping—but the overarching goal remains the estimation of SNP effects. Our intention in focusing directly on the probabilities of causality is to allow us to explore whether established fine-mapping tools can be adapted to the PGS question, benefiting from their speed relative to existing PGS methods.

We present two approaches that can accommodate different assumptions on the number of causal variants in each LD-defined region. The basic fine-mapping approach is very fast because it makes a simplifying assumption that only one causal variant may exist in any LD-defined region, based on the principles developed by Maller et al. (2012). While unrealistic, it has been shown to perform well for fine-mapping and, of relevance to PGS, allows the definition of posterior probabilities of causality using predefined LD regions and without the burden of processing large LD matrices (Maller et al., 2012). Distinguishing noise around null associations from true associations is dealt with by two parameters: a prior probability that a random SNP is causal and the variance of the prior distribution of effect sizes at true causal variants. While in a PGS these would be open to tuning, in fine-mapping sensible default values can be chosen that reflect existing knowledge from the breadth of GWAS studies already conducted (Wallace, 2020).

It is possible to relax the single causal variant assumption if additional information on LD is available. We propose using an alternative fine-mapping method based on the ‘sum of single effects’ model (SuSiE, Wang et al., 2020). SuSiE is a computationally efficient approach to variable selection in linear regression, which uses a multiple causal variant model to compute the posterior inclusion probability for each variant in an LD-defined region, which we can use as \( wi \).

We present RápidoPGS, a lightweight and fast (rápido, in Spanish) method to compute PGS based on fine-mapping approaches that only requires a summary statistics dataset, with no need for an independent test dataset to adjust parameters, and that can generate weights for millions of SNPs in only a few seconds or minutes. RápidoPGS works fully in R, requiring few dependencies. A PGS can be quickly constructed from any GWAS summary statistics dataset, or any GWAS PubMed ID if harmonized datasets are available at GWAS catalog.
Finally, we considered pruning input SNPs according to their P-values using 2 parameters in order to increase speed: (i) $\eta_{block}$, the minimum P-value at least one variant in an LD block must have for the block to be considered for subsequent analyses (i.e. if no SNPs in a block have P-values below $\eta_{block}$, the entire block is skipped), and (ii) $\eta_{SNP}$, the minimum P-value a variant within a selected block must have to be considered.

2.2 GWAS datasets and SNP QC
We downloaded ten publicly available GWAS summary statistics datasets on the following traits: eight case–control datasets: asthma (Demenais et al., 2018), rheumatoid arthritis [RA] (Okada et al., 2014), type 1 diabetes [T1D] (Cooper et al., 2017), type 2 diabetes [T2D] (Scott et al., 2017), breast cancer [BRCA] (Michailidou et al., 2017), prostate cancer [PRCA] (Schumacher et al., 2018), coronary artery disease [CAD] (Nikpay et al., 2015) and major depression disorder [MDD] (Wray et al., 2018). We also added two quantitative traits: body mass index [BMI] (Locke et al., 2015) and height (Wood et al., 2014). All datasets considered are meta-analyses of GWAS performed on European populations, with the exception of RA, which is a trans-ethnic meta-analysis including European and Asian ancestries.

We applied common quality control to all datasets prior to PGS generation by removing unneeded rows with missing data at required columns [genomic coordinates, alleles, allele frequencies, log(OR), standard error], and from case/control sample size column, provided. Following LDpred2 quality control guidance for summary statistics datasets, we computed the effective sample size [Neff = 4/(1/Ne + 1/Nc)], the summary statistic standard deviation (SDstat), defined as $\frac{\text{Neff}}{\sqrt{\text{Neff}}}$, where SE is the standard error of the effect for each SNP, and the validation standard deviation (SDval), which here we computed as $\sqrt{2}(1 - f)$, where f is the allele frequency for the effect allele. When this frequency was not available in the dataset, we computed it using the CEU population in 1000 Genomes Phase III panel. Note that in the LDpred2 paper, SDval is computed using the test dataset, but since our aim is not to identify genetic variants (Supplementary Figs S1–S10).

2.3 PGS generation using RapidoPGS
RapidoPGS comes in two flavours: RapidoPGS-single, and RapidoPGS-multi. As explained in Section 2.1, they correspond to two different approaches, which differ in their assumption of how many causal variants per LD block are considered in their respective results (Supplementary Figs S1–S10).

We further filtered SNPs to the subset overlapping the HapMap3 variants, as recommended by LDpred2, PRScs and SBayesR, the three methods we compared RapidoPGS to. To explore how RapidoPGS prediction ability changes depending on the selection of SNPs, we created another set of post-QC datasets, filtered by 1000 Genomes Phase III variants instead.

2.4 PGS generation using LDpred2-auto
For PGS model generation using LDpred2-auto (Prive et al., 2020) we followed the LDpred2 instructions and adapted the code provided in the tutorials and the accompanying code (https://github.com/privefl/paper-ldpred2 and https://privefl.github.io/bigsnp/articles/LDpred2.html). However, we omitted the prediction steps, as our approach does not consider a test dataset for PGS model generation (see companion code to this paper for implementation details).

We ran LDpred2-auto on a per-chromosome basis for all 22 autosomes.

LDpred2 uses two essential hyperparameters to compute the adjusted effect sizes; $p$ (the proportion of causal variants), and $h^2$ (the heritability of the trait). LDpred2-auto can estimate both hyperparameters from the training data, thus not requiring a test dataset to tune them. For $p$, it can take multiple a number of initial values, from which Gibbs sampling chains run for a fixed number of iterations to find the optimal effect sizes for each SNP. After 4000a number of iterations (3000 after 1000 burn-in), we averaged betas across all chains. As recommended by LDpred2 authors in the LDpred2 tutorial (https://privefl.github.io/bigsnp/articles/LDpred2.html), we used 15 initial values for $p$, ranging from $10^{-4}$ to 0.9. We computed initial $h^2$ from the data using the snp_ldsc function. To ensure convergence, we used 4000 iterations (3000 iterations + 1000 burn-in).

We skipped computation for chromosomes for which estimated $h^2$ was below $10^{-2}$, as was done in the LDpred2 paper (Prive et al., 2020). Note that LDpred2 authors recommend running the genome-wide rather than per-chromosome, due to better performance in their tests. However, LDpred2-auto genome-wide approach did not finish on time for all but one trait (T1D), using 32 hours and 15 CPUs on our HPC. The two approaches for that trait gave very similar results (difference in $r^2 = 0.0031$). Our LDpred2 per-chromosome are also very similar to the reported genome-wide results in LDpred2 paper (Prive et al., 2020). Therefore, we report results for the per-chromosome approach.

2.5 PGS generation using PRScs-auto
We ran PRScs (Ge et al., 2019) using pre-computed LD matrices from European 1000 Genomes Project phase 3 samples, as provided by the authors. We formatted the input summary statistic datasets following documentation and ran PRScs-auto using default parameters. PRScs requires GWAS sample size (N), so we used case + control numbers for case–control datasets. MDD dataset had per-NP N, so we used the sum of median cases and median controls (which were also max values). For BMI and height datasets, which also had per-column N, we used the median value of each dataset as its N (233 691 and 252 021 respectively). We ran PRScs for all chromosomes, and concatenated individual files together. Although it was unclear if PRScs would benefit from parallel computation, we ran it with 15 CPUs and 8 hours for consistency.
2.6 PGS generation using SBayesR
SBayesR is part of the GCTB suite (Lloyd-Jones et al., 2019). SBayesR requires LD matrices from a reference panel too, so we downloaded shrunk sparse LD matrices described in Lloyd-Jones et al. (2019), computed based on a random sample of 50K individuals of European ancestry in UK Biobank data and a genetic map in the public domain, following the algorithm in (Wen and Stephens, 2010). These matrices comprise the HapMap3 variants, like our filtered datasets. SBayesR requires effect allele frequency, and we precomputed them using the CEU population in a 1000 Genomes Phase III panel. We used the same strategy for supplying sample size as we did for PRScs. We experienced some issues related to poor convergence, so following SBayesR documentation advice, we dropped SNPs in the lower 10% N quantile for the three datasets with per-SNP N. We also used the –imputeN flag to allow GCTB estimate per-SNP sample size based on the beta values, SE and allele frequencies and exclude SNPs that have the imputed sample sizes 3 standard deviations apart from the median value. In addition, we used additional –p-value 0.5 –rsq 0.99 flags to remove SNPs with P-values above 0.5 and with r2 larger than 0.99, so mitigating the effect of SNPs in high LD with opposite effects. We ran SBayesR with default values, 15 CPUs and 8 hours. We ran SBayesR for all chromosomes in one go, using –mldm tag and a list of matrices for each chromosome. All datasets ran successfully except for TID, which despite the measures mentioned above continued to experience convergence issues and failed to provide an output.

2.7 Model evaluation using UK Biobank individual data as a validation dataset
We evaluated the predictive performance of our PGS models generated with the four methods using individual genotypes from the UK Biobank cohort. For all traits, we excluded SNPs with low imputation quality (info score <0.3) or multi-allelic SNPs. Moreover, we removed related individuals and restricted the analysis to individuals of European ancestry (UKBB field 22006, genetic ethnic group). The binary traits selected (Supplementary Table S1) were the same used in the evaluation of LDpred2 (Privé et al., 2020) and we applied the same selection criteria for cases and controls as previously described (Privé et al., 2019) following the code for each of the traits as in https://github.com/privefl/simus-PRS/tree/master/paper3-SCT/code_real. For all disease traits, we included as cases those individuals who self-reported the condition or were diagnosed by a medical doctor or the condition was included in their death record. For breast and prostate cancer we excluded individuals with other cancer diagnosis. Moreover, for breast cancer, we restricted the analysis to females, for prostate cancer to males. For rheumatoid arthritis, we excluded individuals with any other musculoskeletal system and connective tissue condition. For type 1 diabetes we excluded individuals with type 2 diabetes and vice versa. For coronary artery disease, we excluded individuals with other heart conditions. For asthma, we excluded individuals with additional respiratory conditions. For MDD we excluded individuals with additional mental and behavioral disorders as well as individuals which were included in the GWAS used to construct the score. The MDD GAW5 we used to generate the score contained ~30 000 individuals from UKBB which corresponded to the initial release and were genotyped with the BiLEVE array. We identified those individuals using code ‘220000’ and excluded those genotyped with the BiLEVE array (batches coded -1 to -11). For BMI and height, we used the UK Biobank codes ‘21001’ and ‘50’, respectively.

After computing the scores, for case–control phenotypes we estimated the area under the curve (AUC) adjusting for the first 40 genetic principal components (PCs, codes ‘22009-0.1-40’), age (code ‘21003-0.0’) and sex (code ‘22001-0.0’)—the latter for all traits except breast and prostate cancer—using the R package ‘ROCGenReg’. We then obtained r2 on the liability scale using the estimated AUC (Lee et al., 2012) as:

\[
r^2_{AUC} = \frac{Q^2}{(m_2 - m)^2 + Q^2m(m - t) + m_2(m_2 - t)}
\]

with:

\[
Q = \Phi^{-1}(AUC)
\]

where m is the mean of liability for cases, K is the population prevalence and t is the threshold on the normal distribution which truncates the proportion of disease prevalence.

\[m_2 = -mK/(1 - K)\]

We estimated K as the proportion of cases from the UKBB dataset.

For continuous traits, we assessed the squared correlation between the PGS and the measured trait (r2) adjusting for the first 40 genetic PCs (codes ‘22009-0.1-40’), age (code ‘21003-0.0’) and sex (code ‘22001-0.0’). Briefly, we regressed each trait against the covariates (PCs, age and sex) and then correlated the residuals with the predictive score for the relevant trait. We constructed 95% confidence intervals for our estimates by bootstrapping 1000 times.

2.8 Runtimes
We timed all methods and approaches for all datasets in independent runs, using the same HPC parameters (i.e. 15 CPUs, 8 hours). We used system.time() function in R for timing RápidoPGS, LDpred2 and SBayesR wall clock runtime. For PRScs, we used the unix ‘time’ programme, as using system.time() was unfeasible.

Times for RápidoPGS includes full PGS generation procedure: check dataset integrity (for both single and multi), handling of precomputed LD matrix or LD matrix computing from panel and z filtering (RápidoPGS-multi only), algorithm running and final weight computation. SBayesR and PRScs require transforming the input data into a specific format, a step we did not include in the timing.

3 Results
We computed PGS for 10 different traits (Table 1, Supplementary Table S1). We first assessed the relative performance of each RápidoPGS approach. For RápidoPGS-multi, we considered two pairs of x parameters for all traits. The milder thinning (SNP= 0.1, Θblock= 10−4) which discards fewer SNPs, showed slightly better performance than SNP= 0.01, Θblock= 10−4 setting, RápidoPGS-multi, which allows for multiple causal variants, achieved better performance than RápidoPGS-single, which is simpler and faster, but has the limitation of assuming a single causal variant per block, which is unrealistic in most scenarios. However, for certain traits (e.g. RA and TID), differences in AUC and r2 for both approaches are small(Fig. 1). Although W (prior variance on the true effect of a variant) can be provided by the user for RápidoPGS-multi, we found that letting RápidoPGS-multi compute W automatically provides better performance, at the expense of increased running time (Supplementary Tables S2 and S3).

We compared the speed of RápidoPGS-single and -multi applying different thresholds, which control the number of input LD blocks and SNPs to construct the PGS (see Section 2). Selecting Θblock=10−4 and SNP=0.01 thresholds which reduces the number of LD blocks and SNPs relative to Θblock=10−3 and SNP=0.1, lowered the run time from ~36% (height) to ~64% (asthma) (Fig. 2).

We next compared RápidoPGS performance with those of LDpred2, PRScs and SBayesR.

RápidoPGS achieved reasonably good prediction performance for most case-control traits, being superior to SBayesR in most instances and reaching prediction values close to PRScs although lower than LDpred2, which showed the best performance for most traits (Fig. 3, Supplementary Table S2). SBayesR experienced convergence issues for TID that we could not fix. RápidoPGS showed poor performance for MDD and both quantitative traits (BMI and Height).
Ra´pidoPGS-multi (a SNP = 0.1, a block = 10/C0) is the best-performing Ra´pidoPGS method, which shows the smallest median r^2 difference and median r^2 ratio to LDpred2 (-0.0092 median difference for case-control, and -0.0429 for quantitative traits, and 0.8011 and 0.6585 median ratio, respectively) and PRScs (mean r^2 difference = -0.0042, and -0.0538, median r^2 ratio = 0.9249 and 0.5863), and outperforms SBayesR for case-control traits (mean r^2 difference = 0.0064 and -0.0436, median r^2 ratio = 1.1787 and 0.6199) (Supplementary Tables S4 and S5).

With regards to runtimes, Ra´pidoPGS-single is the fastest method, being ~8000 to 27 000 times faster than the slowest method for each trait (Fig. 4). Ra´pidoPGS-multi approach involves multiple steps, including SNP filtering, LD matrix computation from panel (if not pre-computed), W automatic estimation, and SuSiE algorithm running. All these steps make it inevitably slower than simpler Ra´pidoPGS-single. Nonetheless, Ra´pidoPGS-multi is generally much faster than any of the other methods (1.12–22.17 times faster). We only observed one instance that Ra´pidoPGS-multi took unusually long to finish (Height in Figs 2 and 4), due to the SuSiE internal algorithm needing to run many iterations to converge in some LD blocks.

4 Discussion

The main downside of most sophisticated PGS methods is their computational cost and running time, taking many hours to finish even when using multiple cores in a high performance computing context. Having PGS scores computed easily and quickly can be advantageous in a context in which there is a need for rapid assessment of many traits. For example, PGS can be used to estimate ‘genetic nurture’ effects on trait values (Balbona et al., 2021) and a search for traits affected by genetic nurture might be more efficient using a two-stage approach: rapid assessment using a Ra´pidoPGS approach,

### Table 1. Training datasets used for PGS computation using four different methods in this study

| Trait | First author | Year | PMID/doi | Controls | Cases | Total | Controls | Cases | Total | Training set | Validation set |
|-------|--------------|------|----------|----------|-------|-------|----------|-------|-------|--------------|----------------|
| BRCA  | Michailidou  | 2017 | 29059683 | 119 078  | 137 045 | 256 123 | 158 385  | 11 578  | 169 963 |
| PRCA  | Schoenmacher | 2018 | 29892016 | 61 106   | 79 148  | 140 254 | 141 551  | 6382    | 147 933 |
| Asthma| Demenais     | 2018 | 29275806 | 107 715  | 19 954   | 127 669 | 261 974  | 43 785  | 305 759 |
| RA    | Okada        | 2014 | 24390304 | 61 565   | 19 234   | 80 799  | 226 320  | 5614    | 231 934 |
| T1D   | Cooper       | 2017 | doi :    |          |         |        |          |        |       |
|       |              |      | 10.1101/ |          |         |        |          |        |       |
|       |              |      | 120022   |          |         |        |          |        |       |
| T2D   | Scott        | 2017 | 28566273 | 132 532  | 26 676  | 159 208 | 314 535  | 14 175  | 328 710 |
| CAD   | Nikpay       | 2015 | 26343387 | 123 504  | 60 801  | 184 305 | 225 917  | 12 263  | 225 917 |
| MDD   | Wray         | 2018 | 29700475 | 113 154  | 59 851  | 173 005 | 255 306  | 22 287  | 277 593 |
| BMI   | Locke        | 2015 | 25673413 | –        | –       | 339 224 | –        | –       | 334 527 |
| Height| Wood         | 2014 | 25282103 | –        | –       | 253 288 | –        | –       | 334 891 |

Note: Validation set refers to the UK Biobank individual data used for PGS evaluation.
followed by a more accurate estimate of that genetic nurture for selected traits using a more accurate PGS, such as LDpred2. Alternatively, in simulation studies to explore the utility of PGS for novel applications, a fast but less accurate method may be preferred for practical reasons.

We have thus developed a method to fill this gap, which comprises two flavours, based on fine-mapping strategies with different assumptions. On the basis of the traits considered here, we recommend using RápidoPGS-multi, as it performs generally better than RápidoPGS-single. For RápidoPGS-multi, we recommend allowing internal estimation of \( \psi \), as it showed to outperform user-supplied \( W \) in most cases (Supplementary Table S1). However, we recommend that when suitable LD information is not available, which is a particular concern in broad-ancestry studies or meta analyses, or when speed is particularly important, that RápidoPGS-single is chosen. Our method for improving the speed of the SuSiE, by filtering SNPs according to \( P \) value, is approximate and was not recommended by the method authors. We use it to allow this fine-mapping approach to run in a reasonable time for our purposes, and it appears to perform well in this situation, but it is unlikely to be optimal. It is possible a more accurate PGS could be constructed if all SNPs were supplied, but this would be at the cost of more than an order of magnitude slower speed.

Like all methods used here for comparison, RápidoPGS-multi requires LD matrices, constructed on the same or similar population to the dataset on which the PGS is trained. However, since individual data is often not available due to privacy concerns, this can be done using a publicly available reference panel. Despite its relatively small size (2504 individuals of worldwide origin), 1000 Genomes Project Phase III is publicly available, and as we have shown, can be used for LD matrix computation and obtain good results. We provide a function to download and pre-process a 1000 Genomes-based reference panel from scratch, although users are free to use their own panel.

We are not the first to suggest that fine-mapping approaches can be helpful for PGS construction, Newcombe et al. (2019) used reversible jump MCMC to fit a fine-mapping model to GWAS summary statistics, parallelising across LD blocks as we do here. However, rather than estimating posterior inclusion probabilities and using these to shrink frequentist effect estimates, they averaged samples from the posterior distribution of causal effect estimates in their fine-mapping model, thus mirroring the PGS approach of focusing on the true effect estimates. Our work offers an alternative method to generate the weights \( u_i \). Other advances in fine-mapping methods may be transferable to the PGS setting. For example, PGS are known to have less predictive power in populations other than that used for training (Martin et al., 2019). This is a particular issue given the euracentric focus of GWAS to date. Restricting PGS to SNPs with known functional annotations has been shown to increase the portability of scores between ancestries (Amariuta et al., 2020), but relevant functional annotations can be incomplete. Fine-mapping offers a natural means to incorporate levels of annotation data through variable per-SNP priors, and methods have been developed to learn appropriate priors through hierarchical Bayesian approaches (Pickrell, 2014). Alternatively, established trans-ancestry fine-mapping approaches may be useful (Morris, 2011). Thus, while our work presents a method designed for fast and easy generation of PGS, it also highlights that the current challenges for PGS may be potentially addressed through adaptation of fine-mapping approaches which addressed similar challenges in that field.

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**Conflict of Interest**: none declared.

**Web resources**

R—https://cran.r-project.org/
RápidoPGS—https://github.com/GRealesM/RapidoPGS
LDpred2—https://privefl.github.io/bigsnpr/articles/LDpred2.html
PRScs—https://github.com/getian107/PRScs
SBayesR—https://csgenomics.com/software/gctv/
LDetect datasets—https://biororket.com/myresearch/ldetect-data/src
GWAS catalog—https://www.ebi.ac.uk/gwas/
1000 Genomes Project—https://www.internationalgenome.org/
LDHub—http://ldsc.broadinstitute.org/ldhub/

Data availability
Summary statistics datasets used are publicly available in their respective publications (see Supplementary Table S1). Code used in the analyses is available at GitLab (https://github.com/GRealesMD/RapidIoPGS_paper) and code used for model evaluation is available at GitLab (https://gitlab.com/evgoritos/applyrapidops).

We have extensively used tools in the bigsnpr (Privé et al., 2018) and datatable packages for large dataset handling and analysis.

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