

Univariate-Guided Sparse Regression for Biobank-Scale High-Dimensional -omics Data

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Abstract

We present a scalable framework for computing polygenic risk scores (PRS) in high-dimensional genomic settings using the recently introduced Univariate-Guided Sparse Regression (uniLasso). UniLasso is a two-stage penalized regression procedure that leverages univariate coefficients and magnitudes to stabilize feature selection and enhance interpretability. Building on its theoretical and empirical advantages, we adapt uniLasso for application to the UK Biobank, a population-based repository comprising over one million genetic variants measured on hundreds of thousands of individuals from the United Kingdom. We further extend the framework to incorporate external summary statistics to increase predictive accuracy. Our results demonstrate that the adapted uniLasso attains predictive performance comparable to standard Lasso while selecting substantially fewer variants, yielding sparser and more interpretable models. Moreover, it exhibits superior performance in estimating PRS relative to its competitors, such as PRS-CS. Integrating external scores further improves prediction while maintaining sparsity.

1 Introduction

With rapid advancements in computing power and storage capacity, data collection has become increasingly detailed and large in scale. As a result, scientists routinely encounter high-dimensional data settings, where the number of predictors is much larger than the number of observations ($p \gg n$). Such scenarios are common in fields like genomics and finance, where granular information can be recorded for each individual or transaction. In these regimes, regression has

become a central tool for both prediction and variable selection, underpinning a wide range of modern applications. A second defining feature of -omics design matrices in particular, is strong correlation among predictors. In genomics, linkage disequilibrium (LD) creates blocks of SNPs that carry very similar information; in transcriptomics, co-expression and shared regulatory programs induce clusters of correlated genes. A truly causal signal at one locus therefore tends to bring along a cloud of correlated predictors with similar univariate behaviour. Any multivariate method must decide what to do with these groups—either select a sparse set of representatives, or distribute (“smear”) the effect across many correlated variables. Although our main focus is on -omics applications, similar large n , larger p structures arise in other domains. In finance, for instance, one may observe long time series or many individual transactions (n) together with hundreds or thousands of asset-, sector-, and macro-level predictors (p), many of which move together through shared risk factors or market regimes. High-dimensional sparse regression in such settings faces the same core challenges: correlated predictors, the need to identify a small subset of informative signals, and stringent computational constraints.

Often, only a much smaller subset of features have a meaningful relationship with the response. Thus a main goal of researchers is to focus on identifying which variables are worth the investment of time and resources to measure and analyze.

1.1 Review of the lasso

The Lasso [Tibshirani, 1996] performs both estimation and variable selection and has become a cornerstone of modern statistics and machine learning.

For a design matrix $X \in \mathbb{R}^{n \times p}$ and response vector $y \in \mathbb{R}^n$, Lasso solves the following minimization problem:

$$\hat{\beta} = \underset{\beta}{\operatorname{argmin}} \frac{1}{2n} \|y - X\beta\|_2^2 + \lambda \|\beta\|_1. \quad (1)$$

λ is a regularization parameter that determines the number of features identified in the solution set. This optimization is typically solved over a grid of λ -values, with the optimal one chosen via cross-validation or by performance of the algorithm on a hold-out validation set. Equivalently, we can formulate the Lasso problem in the following way:

$$\hat{\beta} = \underset{\beta}{\operatorname{argmin}} \frac{1}{2n} \|y - X\beta\|_2^2 \quad \text{subject to} \quad \|\beta\|_1 \leq t \quad (2)$$

where $t > 0$ is a tuning parameter controlling the sparsity of the solution, directly related to λ in the Lagrangian formulation. The constraint sets an upper bound on how large the coefficients $\hat{\beta}$ can be in total (in terms of their ℓ_1 norm, which is $\sum_{j=1}^p |\beta_j|$). A larger t allows the coefficients to grow by imposing a smaller amount of regularization.

1.2 Optimization Approaches for the Lasso

A variety of computational tools have been developed to efficiently solve Lasso problems. `glmnet` [Friedman et al., 2010] is among the most widely cited R packages, capable of computing entire solution paths for a range of generalized linear models. `snpnet` [Qian et al., 2020] is another R package designed specifically for large-scale, high-dimensional Lasso regression in genomics applications. `snpnet` stands out as one of the most competitive solvers, achieving high predictive accuracy in such settings.

Elastic Net (EN) is another path solver that extends the framework by incorporating an ℓ_2 penalty, thereby combining sparsity with ridge regularization. This generalization provides greater flexibility and stability in settings with correlated features, where pure ℓ_1 regularization may perform suboptimally. EN seeks to minimize the following objective function:

$$\hat{\beta} = \operatorname{argmin}_{\beta} \left\{ \frac{1}{2n} \|y - X\beta\|_2^2 + \lambda (\alpha|\beta|_1 + (1-\alpha)|\beta|_2^2) \right\}. \quad (3)$$

Here, $\lambda > 0$ controls the overall regularization strength, while $\alpha \in [0, 1]$ balances the contribution of the ℓ_1 penalty and the ℓ_2 penalty. Setting $\alpha = 1$ recovers the Lasso, while $\alpha = 0$ yields ridge regression. This unified structure allows practitioners to interpolate between the two classical approaches within a single flexible framework.

`Adelie` [Yang and Hastie, 2024] is a novel Python package designed for efficiently solving lasso and group lasso problems. This package can handle large-scale inputs with greater computational efficiency than traditional solvers, and the package provides a suite of generalized linear model (GLM) classes. Benchmarks against other state-of-the-art solvers, such as `glmnet`, demonstrate that `Adelie` achieves faster speeds than other group lasso packages with equivalent accuracy. Additionally, `Adelie` offers flexible parameter tuning, warm-start capabilities, and easy integration with standard Python data science workflows, making it powerful for high-dimensional regression tasks.

Another notable feature of `Adelie` is its ability to efficiently perform regression analyses on genome-wide association study (GWAS) datasets. To handle the scale and complexity of such data, `Adelie` introduces specialized file formats optimized for both memory efficiency and the speed of matrix operations. This design allows the package to process large-scale genotype and phenotype matrices that would otherwise exceed standard memory limits, enabling scalable analyses of GWAS data.

1.3 The UK Biobank Database

The UK Biobank [Bycroft et al., 2018] provides an excellent testbed for scientists using such regression techniques to investigate quantities of interest, such as the variance explained by genomic predictors, and to identify SNPs potentially associated with specific traits. The UK Biobank is a large, population-based repository containing genetic and health information from approximately

500,000 individuals across the United Kingdom. For each participant, it provides data on over 1,000,000 single nucleotide polymorphisms (SNPs) alongside a wide range of phenotypes.

The sheer scale of the UK Biobank introduces substantial computational challenges for analyzing and sparsifying the dataset. Efficient storage and manipulation of this high-dimensional data are pivotal for minimizing objective functions in regression and other statistical models. Recent advances in algorithms and computational tools have made large-scale analyses of datasets of this magnitude increasingly feasible.

Regression provides a natural framework for studying the UK Biobank data, allowing researchers to quantify relationships between SNPs and phenotypes. Packages such as `Adelie` enable analyses to be performed efficiently on such large-scale datasets. By incorporating regularization techniques, i.e. Lasso, regression can produce sparse solutions, effectively reducing the set of over a million SNPs to a smaller subset most likely to be associated with the response. This not only aids in interpretability, but also improves predictive performance by mitigating overfitting in high-dimensional settings.

Polygenic risk scores (PRS) summarize genetic liability as a weighted sum of genome-wide variants. At biobank scale, the standard PRS workflow is two-steps: first, perform a univariate genome-wide association study (GWAS) to obtain marginal effect estimates for each SNP; second, apply an LD-aware shrinkage or selection method (for example, clumping and thresholding, LDpred, or PRS-CS) to convert these marginal effects into a genome-wide predictor. Historically, even this first step already pushed computational limits (fitting millions of univariate regressions on hundreds of thousands of individuals) so genome-wide multivariate regressions were not practically feasible at scale. This computational constraint, together with the complexity of modelling LD explicitly, is a major reason why univariate GWAS has remained the dominant analysis framework for so long. Because GWAS treats each SNP in isolation, a true signal within an LD block typically lifts an entire neighbourhood of correlated SNPs, and without strong shrinkage the naive sum of genome-wide GWAS betas would imply more variance explained than is empirically possible. The second step exists precisely to correct for this double-counting and sampling noise, but it usually leads to dense predictors with highly flattened per-SNP effect sizes.

1.4 Contributions

In this paper, we propose a novel method for analyzing ultra-high-dimensional -omics data that directly fits a sparse multivariate model on individual-level data, rather than relying on the standard two-step GWAS-plus-PRS pipeline. Our work focuses on constructing polygenic risk scores (PRS) from biobank-scale SNP data, where both sparsity and interpretability of selected variants are crucial. We present an adaptation of Univariate-Guided Sparse Regression (uniLasso) [Chatterjee et al., 2025] tailored for this challenging data regime. Empirically, uniLasso achieves predictive performance comparable to existing methods but with 40% fewer predictors, significantly improving the interpretability of

the results. Additionally, we consider the integration of external data sources to further enhance predictive accuracy. In biomedical research, privacy regulations often prevent the sharing of raw data, so researchers sometimes may only provide summary statistics rather than entire data sets.

Following the approach proposed in Chatterjee et al. [2025], we demonstrate how to incorporate external scores from independent datasets into the uniLasso pipeline, bolstering predictions. We show how these external scores can be combined with individual-level data in a single sparse multivariate model, rather than as a separate post-GWAS step.

This paper is organized as follows: Section 2 introduces our adaptation of the uniLasso algorithm, beginning with a brief recap of the standard method before describing how we extend it to both continuous and binary response variables in ultra-high-dimensions. In Section 3 we then demonstrate its practical use through an application to the UK Biobank. We outline how to incorporate external scores and present additional experiments highlighting their benefits in Section 4. Section 5 summarizes comparisons of uniLasso to other approaches for constructing polygenic risk scores. Finally we outline future challenges in Section 6.

2 Proposed Method

2.1 Overview of the uniLasso Algorithm

Univariate-Guided Sparse Regression (uniLasso) [Chatterjee et al., 2025] is a two-stage regression framework that promotes sparsity and interpretability by leveraging information from univariate regressions. Specifically, uniLasso constrains the coefficients in a multivariate model to align with the signs of their corresponding univariate coefficients, enhancing predictive accuracy and improving the interpretability of selected predictors.

The uniLasso procedure, as outlined in Chatterjee et al. [2025], assumes the same supervised learning framework as Lasso. For a design matrix $X \in \mathbb{R}^{n \times p}$ and response vector $y \in \mathbb{R}^n$, the uniLasso procedure is defined as follows:

1. For $j = 1, 2, \dots, p$ compute the univariate intercepts and slopes $(\hat{\beta}_{0j}, \hat{\beta}_j)$ and their leave-one-out (LOO) counterparts $(\hat{\beta}_{0j}^{-i}, \hat{\beta}_j^{-i})$, $i = 1, \dots, n$. Compute the LOO fitted values for all i and j and aggregate them in a new $n \times p$ feature matrix F .
2. Fit a non-negative Lasso with an intercept and no standardization to target y and the univariate LOO predictions as features:

$$\operatorname{argmin}_{\theta} \left\{ \frac{1}{n} \sum_{i=1}^n \left(y_i - \theta_0 - \sum_{j=1}^p (\hat{\beta}_{0j}^{-i} + \hat{\beta}_j^{-i} x_{ij}) \theta_j \right)^2 + \lambda \sum_{j=1}^p \theta_j \right\}$$

subject to $\theta_j \geq 0, \forall j > 0$. Select λ through cross validation.

3. The final model can be written as

$$\hat{\eta}(x) = \hat{\gamma}_0 + \sum_{j=1}^p \hat{\gamma}_j x_j,$$

with $\hat{\gamma}_j = \hat{\beta}_j \hat{\theta}_j$, and $\hat{\gamma}_0 = \hat{\theta}_0 + \sum_{\ell=1}^p \hat{\beta}_{0\ell} \hat{\theta}_\ell$.

Note that we do not standardize the features before applying the non-negative Lasso in Step 2 because the entries of F are all on the scale of the response. Closed-form expressions for the LOO fits and the univariate coefficients are provided in Section 2.2.

The steps taken in this procedure serve several purposes. First, it ensures that the signs of the final coefficients agree with the signs of the univariate coefficients (or they are zero). This increases the interpretability of the result, as it excludes features whose coefficient sign changes between the univariate and multivariate model. In addition, features with larger univariate coefficients will also tend to have larger coefficients in the final model. Moreover, using LOO fitted values rather than raw univariate estimates or the original features amounts to feeding cross-validated univariate predictions into the Lasso in Step 2. This forces the selection step to rely on out-of-sample predictive signal rather than in-sample noise, which empirically leads to sparser models and improved generalization. [Chatterjee et al., 2025].

As demonstrated in the uniLasso paper, this method has exhibited excellent performance, producing sparser solutions than classical techniques. However, many challenges emerge when applying the algorithm in the high-dimensional regime. In its original formulation, however, uniLasso is not immediately scalable to biobank-sized datasets, which prevents a direct comparison with genomics tools such as `snpnet`.

As discussed above, one challenge of ultra-high-dimensional data analysis is the need to store the immense feature matrix. In computation, Step 1 of the uniLasso pipeline actually requires the user to remember another $(n \times p)$ matrix of the LOO fitted values. While SNP matrices are typically sparse (many of the entries are 0), the LOO matrix F is not. Thus the computer must be capable of storing another feature matrix which could take up over 1500 GB of memory.

Computation time arises as a second challenge when calculating the univariate coefficients and LOO fitted values. Since they need to be computed for each column, when the number of covariates is in the order of millions (as is the case in -omics settings) this procedure can take a long time.

A final challenge arises in Step 2 of the algorithm when choosing the regularization value. Again, given the scale of the data, cross validation becomes computationally infeasible. This is because each of the k folds requires refitting the model on a large proportion of the entire dataset, leading to prohibitively large computational, memory, and time costs.

2.2 Details of the Omics-adapted uniLasso Algorithm

To address the computational challenges discussed above, we propose a modified version of the uniLasso algorithm designed for application in general -omics settings. We demonstrate that this method achieves predictive performance comparable to standard tools such as `snpnet`, while producing substantially sparser and more interpretable solutions.

We utilize Sherlock, a high-performance computing (HPC) cluster at Stanford University, to engineer the uniLasso pipeline using the `Adelie` Python package. Our compute instances use a cluster of Intel(R) Xeon(R) E5-2640 v4 CPUs with 64 total cores. This setup enables efficient allocation of memory and computational resources necessary to sustain the full analysis. When calculating the leave-one-out (LOO) fits and univariate coefficients, it is important to note that each computation depends only on individual columns of the design matrix.

For a given SNP column x_i , let $x_c = x_i - \bar{x}$, where \bar{x} denotes the column mean. Similarly, define y_i as the response and $y_c = y_i - \bar{y}$ as its centered counterpart. The univariate slope u_1 and intercept u_0 are then given by:

$$u_1 = \frac{x_c^T y_c}{x_c^T x_c}, \quad u_0 = \bar{y} - u_1 \cdot \bar{x}.$$

The LOO fitted values L for the same column x_i can be computed as follows, where H_{ii} denotes the i^{th} diagonal element of the hat matrix H :

$$L = y_i - \frac{y_i - (u_0 + u_1 x_i)}{1 - H_{ii}}, \quad \text{where } H_{ii} = \frac{1}{n} + \frac{x_c \odot x_c}{x_c^T x_c}.$$

Using vectorized formulas we parallelized the computations, which occur in an embarrassingly parallel manner. This allowed us to fully exploit CPU resources and parallel computing to markedly accelerate computation.

In the standard uniLasso algorithm, the regularization parameter in Step 2 is typically chosen via k -fold cross validation. However, once again given the scale of our data, this approach is computationally infeasible. Instead, we employed a train-validation-test split (70/10/20) to efficiently tune the regularization strength. Specifically, we first fit the model on the training set over a grid of λ values. Using the validation set, we then identified the value of λ that achieved the best predictive performance. Next, we refit the model on the combined training and validation sets with the chosen parameter. Finally, we evaluated the resulting model on the held-out test set to obtain the optimal coefficients.

This validation-based approach substantially reduced computational time and the need to store large amounts of data, while yielding empirically strong results. We also believe that this strategy is an effective and generalizable approach for hyperparameter tuning in ultra-high-dimensional settings.

Moreover, SNP data is known to be particularly sparse, typically taking values in the set $\{0, 1, 2\}$. Typically, a majority of the entries in a given column

of a SNP feature are 0. To address the small levels of variance within certain column, we implemented two strategies:

1. Minor allele frequency (MAF) filtering:

Minor allele frequency (MAF) is the proportion of the less common allele among all observed alleles at each SNP. SNPs with MAF below 0.0005 were excluded prior to applying uniLasso (or Lasso). This filtering step is standard in genomic analyses, as rare variants tend to contribute little predictive power and can lead to unstable coefficient estimates.

2. Stabilizing regularization of low-variance columns:

For SNPs with $\text{MAF} \geq 0.0005$, small variances still occasionally caused univariate coefficients to explode, leading to unstable estimates. One key quantity that appears in the denominator of the univariate and LOO calculations is

$$S_{xx} = x_c^T x_c, \quad \text{where } x_c = x - \bar{x}.$$

Tusher et al. [2001] encountered a similar instability in the context of microarray analysis, where small denominators led to highly variable test statistics. They propose adding a data-dependent constant to stabilize the denominator. Following this approach, we regularize low-variance SNP columns by replacing S_{xx} with

$$S_{xx}^* = S_{xx} + \text{fifth-percentile}(S_{xx}),$$

where the additive constant corresponds to the fifth percentile of the empirical distribution of S_{xx} values over all columns of the SNP matrix. This adjustment prevents unstable estimates arising from sparse or near-constant genotype columns when S_{xx} approaches zero.

Both modifications substantially improved stability across data partitions and, in most cases, even enhanced predictive performance relative to non-regularized runs.

2.3 Omics-adapted uniLasso Algorithm for Binary Response Variables

In the case where the response variable is binary rather than continuous ($y_i \in \{0, 1\}$ for all i), we use a penalized logistic regression objective function:

$$\hat{\beta} = \underset{\beta}{\operatorname{argmin}} \left\{ -\frac{1}{n} \sum_{i=1}^n [y_i \log p_i + (1 - y_i) \log(1 - p_i)] + \lambda \sum_{j=1}^p |\beta_j| \right\},$$

where $p_i = \frac{\exp(\beta_0 + x_i^\top \beta)}{1 + \exp(\beta_0 + x_i^\top \beta)}$.

Similar to the Lasso, we introduce regularization to control the sparsity of the solution.

For uniLasso, recall that the algorithm requires LOO fitted values and univariate coefficients. Unlike the case with Gaussian loss, however, there are no closed-form solutions for these expressions. However, in practice, logistic regression is typically fit via iteratively reweighted least squares (IRLS). Given the fitted linear predictor vector $\eta_j^{(\ell)}$ at iteration ℓ , one forms a working response vector $z_j^{(\ell)}$ that depends on $\eta_j^{(\ell)}$, y , and the GLM family, along with an observation weight vector $w_j^{(\ell)}$. The updated model $\eta_j^{(\ell+1)}$ is then obtained by performing weighted least squares of $z_j^{(\ell)}$ on x_j with weights $w_j^{(\ell)}$. In our implementation, we perform two IRLS iterations per feature.

As in the Gaussian setting, we parallelize and vectorize operations to efficiently fit all p univariate logistic regression models. The expressions are only slightly more complex than in the unweighted case. For the LOO fits, we adopt the approximation proposed by Rad and Maleki [2020], which provides estimated LOO predictions without refitting and has been shown to work well in large-scale GLM applications. This corresponds to using the final weighted least squares IRLS iteration from each univariate fit when fitting the univariate models. We use the formula they propose which accommodates observation weights.

Finally, we apply the same regularization and MAF filtering when running the binary uniLasso algorithm. Aside from the modifications required for the logistic loss and the corresponding univariate values, the majority of the uniLasso pipeline remains nearly identical to the Gaussian case.

3 UK Biobank Analysis

We describe a real-data application on the UK Biobank that demonstrates the utility of the uniLasso algorithm.

The UK Biobank [Bycroft et al., 2018] is a large prospective cohort study containing extensive genetic and phenotypic data from approximately 500,000 middle-aged individuals across the United Kingdom. In this analysis, we focus on modeling the relationship between individual genotype sequences and their corresponding phenotypic traits. Using uniLasso, we aim to identify SNPs that are most strongly associated with the phenotype of interest. Our proposed adaptation enables model fitting at full scale and yields a reduced active variable set compared to alternative methods. This smaller collection of selected SNPs enhances interpretability while maintaining comparable levels of variance explained.

We restricted our analysis to a subset of 336,442 White British individuals from the full UK Biobank dataset who satisfy the population stratification criteria described in DeBoever et al. [2018]. The data were randomly partitioned into training (70%), validation (10%), and test (20%) subsets. Each individual has 1,080,968 measured genetic variants, where each variant is encoded by one

Number of Non-Zero Coefficients				
Model	Height	BMI	CHD	Asthma
Lasso	55,038	33,076	2,615	5,556
uniLasso	34,256	18,833	1,009	3,030
uniLasso ES	44,788	24,598	1,310	5,698

Table 1: *Number of non-zero coefficients for each phenotype measured across all Lasso-based algorithms. Compared to Lasso, uniLasso selects 38% fewer SNPs for height and 43% fewer for BMI, while only reducing R^2 by 0.006 and 0.016, respectively.*

of three levels: 0 for homozygous major alleles, 1 for heterozygous alleles, and 2 for homozygous minor alleles. Missing genotypes were imputed using the mean of the observed values. In addition to genotype data, covariates such as age, sex, and 10 precomputed principal components of the SNP matrix were included to account for population structure. Among the thousands of measured phenotypes in this dataset, the phenotypes we used to evaluate our method were standing height, body mass index (BMI), coronary heart disease (CHD), and asthma. CHD and asthma are binary responses, where 0 indicates a lack of the disease and 1 delineates individuals who do suffer from the disease.

To evaluate predictive performance for the continuous responses, we use the R^2 statistic: given a linear estimator $\hat{\beta}$ and data (y, X) , R^2 is defined as

$$R^2 = 1 - \frac{\|y - X\hat{\beta}\|_2^2}{\|y - \bar{y}_0\|_2^2},$$

where \bar{y}_0 is the average response of the training data. In this setting, the PRS for individual i is the linear predictor $\widehat{\text{PRS}}_i = x_i^\top \hat{\beta}$, where x_i denotes that individual's vector of SNP genotypes. This metric represents the proportion of variance explained by the covariates. Ranging from 0 to 1, higher values represent better explanatory power by the model. We evaluate this criteria for all models fit on continuous response variables.

For binary responses, we assess predictive performance using the receiver operating characteristic (ROC) curve, which illustrates the trade-off between true and false positive rates across different classification thresholds. The area under the ROC curve (AUC) reflects how well the model distinguishes between positive and negative outcomes, with higher values corresponding to improved performance. For phenotypes with binary outcomes, we evaluate the AUC for all regression methods used.

We perform Lasso and uniLasso on all of the aforementioned phenotypes to have a sense of any potential advantages. For the continuous phenotypes (height and BMI) there is a consistent trend: Lasso outperforms uniLasso by a small margin but uses a significantly larger number of coefficients in its solution. The small loss in R^2 is worthwhile for uniLasso when considering the nearly

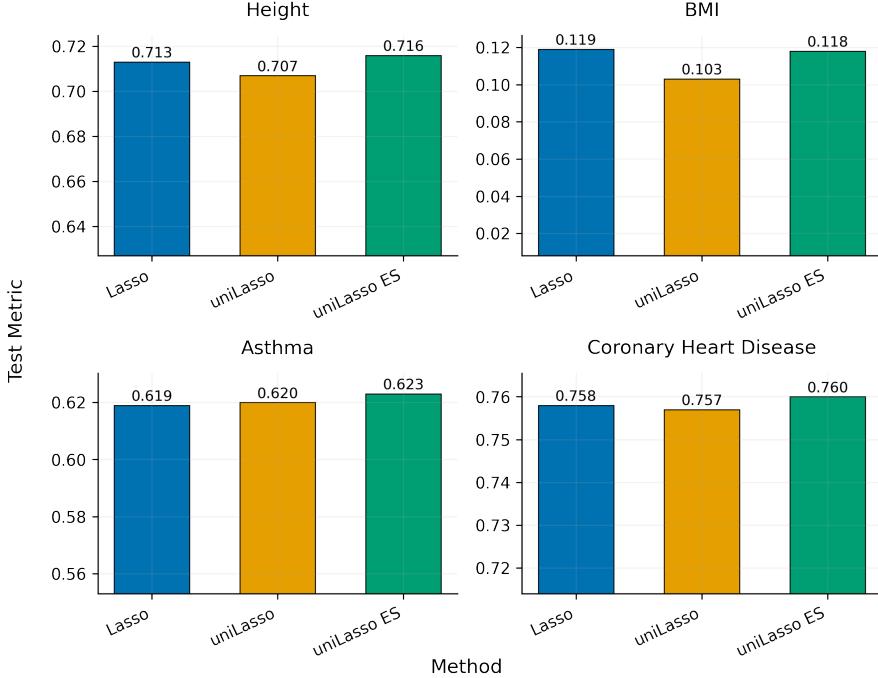


Figure 1: *Comparison of the test set predictive performance of the different polygenic risk score (PRS) methods with refitting on the training and the validation set.* All regressions were performed with Adelie in Python. R^2 are evaluated for the continuous phenotypes (height and BMI), and AUC evaluated for the binary phenotypes (asthma and CHD).

40% reduction in active set size. Figure 1 illustrates the difference in their performance on held out test sets while Table 1 displays the number of non-zero coefficients at the optimal λ value for each method tested on each phenotype.

In the binary case, uniLasso and Lasso perform much more similarly when measured in AUC, with uniLasso even outperforming Lasso on Asthma. Otherwise, the difference in test error between Lasso and uniLasso does not exceed 0.016, an encouragingly small margin. Excitingly, as also seen with the continuous responses, uniLasso maintains a significantly sparser solution set than Lasso. For CHD, uniLasso is over 50% sparser than Lasso and has lower test error by only 0.001. UniLasso is consistently the best performing under this sparsity metric. This reduced solution set in conjunction with the alignment of signs between univariate and multivariate coefficients reinforces the merits of uniLasso. Section 4 goes into more detail about an alternative formulation of uniLasso that potentially achieves a more optimal tradeoff.

Table 2 summarizes the number of sign changes observed between the univariate coefficients and the non-zero coefficients in the final Lasso model. This

Number of Sign Changes in Lasso		
Phenotype	Num.	Sign Changes
Height	6,698	
BMI	103	
CHD	2	
Asthma	2	

Table 2: *Number of coefficient sign changes between the univariate and multivariate models for each phenotype. UniLasso, by construction, eliminates all such sign reversals; every non-zero coefficient retains the sign of its univariate effect.*

metric reflects the interpretability of the multivariate (Lasso) model: solutions with sign changes indicate that the multivariate fit has flipped the direction of association for certain variables. Such reversals are difficult to interpret because they obscure the role each variable plays in predicting disease susceptibility (or any other phenotype); the meaning of a coefficient’s sign becomes context-dependent, which is particularly ambiguous when dealing with SNPs. As shown in the table, the binary models exhibit far fewer sign changes than the continuous ones, which is expected given their smaller active sets. A built-in advantage of uniLasso is the lack of sign changes regardless of the type of response variable.

4 Use of External Scores

Our second contribution addresses the integration of external data to enhance predictive accuracy. In biomedical research, privacy regulations often restrict the sharing of raw individual-level data, meaning that researchers may only provide summary statistics rather than full datasets. Chatterjee et al. [2025] proposed a method for incorporating external univariate scores from an independent dataset, denoted \mathbf{E} , into the uniLasso pipeline.

A collaborator from Finland provided external summary statistics from FinnGen, the Finnish counterpart to the UK Biobank, which comprises approximately 500,000 participants. The external scores from FinnGen consist of the results of univariate SNP regressions that include age, sex, and the first ten principal components as covariates.

We begin by computing the univariate intercepts and slopes $(\hat{\beta}_{0j}, \hat{\beta}_j)$, as in Step 1 of uniLasso. However, rather than relying on the standard formulation that uses leave-one-out (LOO) coefficients, Chatterjee et al. [2025] propose an alternative regression framework, presented as equation (3.3) in their paper:

Similarity	Height	BMI	CHD	Asthma
L and U	0.27	0.29	0.29	0.36
L and E	0.20	0.18	0.07	0.10
U and E	0.23	0.22	0.09	0.11

Table 3: *Proportion of shared nonzero coefficients between each pair of models (Lasso (L), uniLasso (U), and uniLasso with external scores (E)) for all phenotypes. Each value represents the size of the intersection divided by the size of the union of non-zero SNPs.*

$$\operatorname{argmin}_{\gamma} \sum_{i=1}^n (y_i - \gamma_0 - \sum_{j=1}^p x_{ij} \gamma_j)^2 + \lambda \sum_{j=1}^p \frac{|\gamma_j|}{|\tilde{\beta}_j|} \quad \text{s.t. } \operatorname{sign}(\gamma_j) = \operatorname{sign}(\tilde{\beta}_j) \forall j \quad (4)$$

The idea is to use the univariate coefficients from \mathbf{E} rather than compute the LOO estimates from the training data. In the equation above these correspond to the $\tilde{\beta}_j$ terms. Specifically, the magnitudes $|\tilde{\beta}_j|$ serve as adaptive weights in the ℓ_1 -penalty term, while the signs of $\tilde{\beta}_j$ agree with the signs of the estimated coefficients γ_j (or they are zero). We draw the univariate slopes and intercepts from the UK Biobank training data, but use the external coefficients $\tilde{\beta}_j$ to define the adaptive penalty weights and sign constraints in the second-stage regression.

The final model can be written as $\hat{\eta}(x) = \hat{\theta}_0 + \sum_{j=1}^p \hat{\theta}_j x_j$, with $\hat{\theta}_j = \tilde{\beta}_j \hat{\gamma}_j$, and $\hat{\theta}_0 = \hat{\gamma}_0 + \sum_{\ell=1}^p \hat{\beta}_{0\ell} \hat{\gamma}_\ell$. Here, we reincorporate the univariate slopes and intercepts from the first stage to obtain the final fitted model. The parallels with the standard uniLasso formulation are apparent. Note this alternative construction holds for binary responses as well.

The results for uniLasso with external scores (denoted uniLasso ES) are displayed alongside those of Lasso and standard uniLasso in Figure 1. uniLasso ES achieves the highest predictive performance across all phenotypes evaluated except for a negligible 0.001 difference with Lasso for BMI. Compared to uniLasso, it appears that external scores will always boost the predictive power of the model. Although the resulting models are slightly less sparse than those from standard uniLasso, they remain consistently sparser than Lasso (again, see Table 1). The solution set for CHD is also very nearly 50% sparser than Lasso in this framework. These findings demonstrate that incorporating external scores enhances both accuracy and interpretability, yielding models that outperform the ubiquitous Lasso in predictive power and sparsity.

Table 2 shows that the logistic models exhibit very few sign changes. This naturally leads to examining how much alignment there is among the sets of selected SNPs across methods. Table 3 reports the sizes of each pairwise intersections divided by the size of their union. We examine the overlaps between Lasso, uniLasso, and uniLasso ES. Across all phenotypes, Lasso and uniLasso share the largest overlap, followed by Lasso and uniLasso ES. Lasso and uni-

Phenotype	Lasso	uniLasso	uniLasso ES	PRS-CS
Height	0.713	0.707	0.716	0.649
BMI	0.119	0.103	0.118	0.070
Asthma	0.619	0.620	0.623	0.596
CHD	0.758	0.757	0.760	0.760

Table 4: *Test set predictive performance of the four PRS methods for each phenotype. For Height and BMI, the metric is R^2 ; for Asthma and Coronary Heart Disease (CHD), the metric is AUC.*

Lasso exhibit their largest similarity for the binary traits.

5 Comparison of uniLasso to Other Approaches

In this section we summarize the performance differences among the methods considered. In addition to the three Lasso-based methods we analyze PRS-CS [Ge et al., 2019], a summary statistics-based Bayesian regression method. PRS-CS computes polygenic risk scores using GWAS summary statistics and an external LD reference panel, but it neither incorporates *external* summary statistics nor induces sparsity in its effect-size estimates. For PRS-CS, we first generated GWAS summary statistics on the combined training and validation ($n = 269,711$) with age, sex, and the top 10 PCs as covariates using PLINK v2.0a7 [Chang et al., 2015, Purcell and Chang, 2020]. We then applied PRS-CS with default settings using the precomputed European-ancestry LD reference panel derived from the 1000 genomes samples (PRScs GitHub Repo). Finally, we extracted the posterior effect-size estimates and computed polygenic risk scores using PLINK2’s `--score` subcommand [Chang et al., 2015].

PRS-CS underperforms the three Lasso-based methods on three of the four phenotypes and matches uniLasso ES on CHD (see Table 4). Combined with its higher computational cost and lack of sparsity, this limits its suitability for settings where interpretability is important. This makes it harder to gain any intuition behind which variants are actually driving the signal.

See Appendix A for a discussion regarding the difference in runtimes for each algorithm.

6 Discussion

In this paper, we propose a new framework for analyzing ultra-high-dimensional omics data. Our approach builds on the univariate-guided sparse regression (uniLasso) algorithm recently introduced by Chatterjee et al. [2025]. More broadly, our work demonstrates how uniLasso can be adapted into a practical framework for biobank-scale PRS construction and how external summary statistics can be integrated into such pipelines. Using the Python package

Adelie, we implement polygenic risk score (PRS) algorithms for both continuous and binary outcomes.

We evaluate our methods on SNP data to demonstrate their gains in sparsity and interpretability over existing approaches. Our experiments indicate that uniLasso achieves about 40% more sparsity than Lasso while maintaining comparable predictive performance. Furthermore, integrating external data into the framework yields a noteworthy improvement in prediction accuracy. In the UK Biobank application, uniLasso with external scores (uniLasso ES) achieves the best or nearly best predictive performance across all four phenotypes. Additionally, uniLasso ES retains substantially fewer non-zero coefficients than Lasso and far fewer than PRS-CS, which keeps all SNPs in the model.

Across all settings, uniLasso’s enforced sparsity enables efficient computation in ultra-high-dimensional regimes while preserving, and often improving upon, the predictive accuracy of dense alternatives. It is particularly striking that for height, a canonical highly polygenic trait, our best uniLasso models rely on only 30,000 – 40,000 non-zero SNPs out of more than one million candidates, yet still achieve test $R^2 \approx 0.71$, clearly outperforming PRS-CS on the same dataset. Despite the extensive LD structure across the genome, uniLasso appears able to concentrate predictive signal onto a comparatively small subset of variants or LD blocks. This pattern is consistent with a view in which much of the SNP-heritability is effectively compressed into a modest number of genomic locations, even for traits that are often described as “highly polygenic”.

From this perspective, our results provide an empirical counterpoint to strictly “pangenomic” or infinitesimal models in which every variant is assumed to have a non-zero effect. Dense approaches like LDpred-inf and PRS-CS remain valuable, especially when only GWAS summary statistics are available, but our findings suggest that (at least for traits like height) there is little predictive benefit in keeping millions of non-zero coefficients once LD and sample size are properly accounted for. A sparse-polygenic view, where a few tens of thousands of variants capture most of the predictive signal, appears sufficient for practical prediction in this setting. Methods such as PRS-CS or infinitesimal-prior approaches effectively assume that every variant has a non-zero effect, but that most effects are very small. In the presence of LD, these dense models spread each signal over many correlated SNPs, so that each individual predictor carries a heavily shrunk, “flattened” effect size. This is attractive for aggregate prediction and some forms of inference, but it makes it difficult to identify which specific variants or LD blocks are truly driving the score. Moreover, for individual-level risk prediction, relying solely on correlated tag SNPs has a causal cost: whenever the LD between tag and causal variant is imperfect, individuals whose genotypes deviate from the dominant LD pattern receive contributions from non-causal predictors that are essentially noise. In contrast, a sparse multivariate method that concentrates weight on (or near) truly causal variants aims to reduce this mismatch between the mechanistic signal and the predictors used for stratification, potentially improving both interpretability and robustness of individual risk estimates.

More broadly, our comparisons highlight a generic tension in LD-structured

high-dimensional regression. Traditional GWAS is purely univariate, so each SNP’s marginal effect conflates its own contribution with that of its correlated neighbors. Dense multivariate models that do not explicitly promote sparsity tend to share this signal across entire correlated sets, yielding many predictors with tiny, flattened effect sizes. In contrast, the ℓ_1 penalty and sign constraints in uniLasso force the model to choose a subset of SNPs to carry the signal within each LD block, leading to larger, more interpretable per-variant effects without sacrificing out-of-sample prediction.

There are a number of associated challenges that we plan to pursue as a natural consequence of this work. The existing uniLasso framework handles $K = 2$ -class targets but not $K > 2$. This is an inherently difficult problem since the K coefficients for each feature are shift-invariant and hence their signs are not meaningful. We intend to develop and test new forms of uniLasso in the multiclass (multinomial) response context. A second extension concerns applying uniLasso to sets of SNPs found from linkage disequilibrium (LD)-based pre-clustering (e.g., via clumping or pruning) and studying the resulting false discovery rate. There is recent work along these lines using Lasso which suggests this is a promising domain. Moreover, leave-one-chromosome-out (LOCO) cross-validation may help avoid signal leakage through LD and polygenic signals. Implementing LOCO folds within uniLasso could provide more reliable model assessment in genetic applications.

Finally, we are interested in developing a version of uniLasso that simultaneously incorporates both LOO fitted values and external univariate scores. As of now, uniLasso and uniLasso ES each leverage only one of these information sources; a unified approach that blends them could yield further gains in stability, sparsity, and predictive accuracy. Such a method would be especially valuable in large-scale genomic settings like the UK Biobank.

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We will soon make available a Python package “Lasso-PRS” implementing both Lasso and uniLasso for polygenic risk scores.

Appendix

A Algorithmic Runtimes

Method / Stage	Continuous Response	Binary Response
<i>Preprocessing</i>		
uniLasso (pretraining)	90 min	4 hr
<i>Training Time</i>		
Lasso	2.5 hr	85 min
uniLasso (after pretraining)	3 hr	5 hr
uniLasso ES	1.5 hr	35 min
PRS-CS	5.5 hr	5.5 hr

Table 5: *Approximate computation times for model training across all methods. Standard uniLasso includes an additional preprocessing stage in which the the LOO fitted values and univariate coefficients are computed for each feature.*

An important practical consideration is the training time required for each algorithm, summarized in Table 5. All computations were performed on Stanford University’s high-performance computing cluster, Sherlock. For continuous outcomes, the preprocessing stage of uniLasso, which computes the leave-one-out (LOO) fitted values and the univariate coefficients, takes roughly 90 minutes on 64 CPUs for a dataset of size roughly about 250,000 individuals and 710,000 SNPs. For binary responses, the preprocessing runtime increases to around 4 hours due to the additional iterative approximation required in the IRLS optimization.

Fitting the uniLasso model with Gaussian loss after the computation of the pretraining values required approximately 3.5 hours. This is slightly longer than the average of 2.5 hours for Lasso, which in turn is greater than the 1.5 hour average for uniLasso with external scores (uniLasso ES). The reduced runtime of uniLasso ES arises from its formulation, which preserves the sparsity of the SNP matrix rather than populating it with dense LOO fitted values, as in the standard uniLasso implementation.

Training becomes even quicker when modeling binary outcomes. Under the same parameter configurations, Lasso finishes fitting in approximately 85 minutes, while uniLasso ES converges in only about 35 minutes. This exceptionally fast runtime further highlights the advantages of the uniLasso ES formulation. On the other hand, standard uniLasso requires an additional 5.5 hours of training after computing the necessary univariate and LOO estimates. With appropriate computational resources, for example GPU acceleration, this time could be substantially reduced. This is a direction we are actively pursuing. Nonetheless, the longer runtime is offset by the interpretability and unprecedented sparsity of the resulting model.

Across all response types, uniLasso with external scores achieves the fastest average training time among sparsity inducing competitors. This highlights the advantage of leveraging external information within the uniLasso framework, which reduces the need for intensive pretraining computations.

The PRS-CS pipeline involves substantial preprocessing and data formatting before the main model can be run, and additional steps are required afterward to aggregate the scores into a usable test metric. On Stanford’s Sherlock cluster, the primary PRS-CS Python command took roughly 5.5 hours to run, regardless of phenotype (Table 5). In our experiments it showed somewhat weaker predictive performance compared to the Lasso-based methods, and does not naturally yield sparse models.

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