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Statistical methods for gene–environment interaction analysis

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Abstract

Most human complex phenotypes result from multiple genetic and environmental factors and their interactions. Understanding the mechanisms by which genetic and environmental factors interact offers valuable insights into the genetic architecture of complex traits and holds great potential for advancing precision medicine. The emergence of large population biobanks has led to the development of numerous statistical methods aiming at identifying gene–environment interactions (G × E). In this review, we present state-of-the-art statistical methodologies for G × E analysis. We will survey a spectrum of approaches for single-variant G × E mapping, followed by various techniques for polygenic G × E analysis. We conclude this review with a discussion on the future directions and challenges in G × E research.

Keywords

gene–environment interaction (G × E); precision medicine; statistical genetics

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AUTHOR CONTRIBUTIONS

Jiacheng Miao: Conceptualization (lead); methodology (lead); writing – original draft (lead); writing – review and editing (lead). **Yixuan Wu:** Formal analysis (supporting). **Qiongshi Lu:** Conceptualization (lead); funding acquisition (lead); project administration (lead); writing – review and editing (lead).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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1 | INTRODUCTION

Genetic variations, environmental factors, and their interactions jointly shape human complex phenotypes (Freeman, 1973). Understanding gene–environment interaction (G × E) can provide crucial mechanistic insights into genetic and environmental effect heterogeneity (Li et al., 2019). One recent example of G × E finding in humans is the interaction between *BAP1* and asbestos exposure in mesothelioma (Carbone et al., 2020). In Cappadocia, Turkey, an asbestos-like carcinogenic fiber was found in the homes and air of villagers. However, this environmental exposure alone could not explain an epidemic in which 50% of the villagers died of mesothelioma, especially compared with only 4.6% of asbestos miners with at least 10 consecutive years of work (Carbone et al., 2007). Studies of the epidemic in Cappadocia led to the discovery that susceptibility to mesothelioma is passed down through generations in a Mendelian pattern and is caused by a G × E interaction (Carbone et al., 2020). Other notable human G × E examples include the interaction between *FTO* and physical activity on body mass index (Young et al., 2016), the interaction between *SLC2A9* and biological sex on uric acid concentrations (Döring et al., 2008), and the interaction between the genetic risk of obesity and education on health-related outcomes (Barcellos et al., 2018). However, these are the few well-characterized G × E examples in humans. Way too often, the environment is ignored in human complex trait genetic studies. It also largely remains an open problem how such interactions should be modeled, quantified, and estimated in current study designs.

Early investigations into G × E primarily relied on a candidate gene approach (Caspi et al., 2003), which suffered from low replicability (Dick et al., 2015). The emergence of high-throughput genotype data enabled the implementation of genome-wide interaction studies (GWIS), allowing for comprehensive G × E scans across millions of single nucleotide polymorphisms (SNPs; Thomas, 2010). While GWIS improves the replicability and robustness of interaction findings, it poses challenges in terms of the burden of multiple testing, which substantially limits its statistical power (Aschard et al., 2012). To address this limitation, a two-step approach has been employed, involving an initial SNP filtering, followed by testing G × E exclusively on selected SNPs. However, it is now widely recognized that most human complex traits exhibit a highly polygenic nature (Boyle et al., 2017). Consequently, contemporary GWAS analyses have shifted focus away from individual SNPs, embracing methodologies that account for the polygenic nature of these traits (Bulik-Sullivan et al., 2015; Finucane et al., 2015; Miao et al., 2023). Similarly, G × E studies are undergoing a similar transition, placing greater emphasis on understanding how the polygenic basis of a trait varies across different environments (Arold et al., 2022; Barth et al., 2020; Bernabeu et al., 2021; Dahl et al., 2020; Martin et al., 2021; Robinson et al., 2017).

This article aims to comprehensively examine the cutting-edge statistical methods employed in G × E inference using molecular data. In the subsequent sections, we will begin by providing an overview of the fundamental concept of G × E. Then, we will review and compare statistical methodologies utilized for single-variant G × E studies as well as polygenic G × E inference. We will conclude this article by discussing the prospects and prevailing challenges of G × E analysis. Figure 1 presents a decision tree to guide the selection of an appropriate method for G × E inference. Table 1 offers the links to the methods and tools in this review.

2 | DEFINING G × E

G × E is commonly defined as the joint effect of genetics and the environment that deviates from their individual additive effects (Freeman, 1973). This concept is illustrated in Figure 2. Figure 2a illustrates a scenario where carrying an additional A allele produces a consistent change in the phenotype across different environments, suggesting the absence of G × E. Conversely, in Figure 2b, the presence of an additional A allele leads to varying changes in the phenotype across the environments, indicating the presence of G × E.

The estimation problem for G × E can be formulated within the following statistical framework. We consider a generalized linear model that incorporates the main effects of genetics and the environment, along with their interaction:

$$g(E[Y_i \mid G_i, E_i]) = \beta_0 + \beta_G G_i + \beta_E E_i + \beta_I G_i E_i$$

where subscript i denotes the ith individual, g is the link function, Y_i is the phenotype, E_i is an environmental factor, G_i is the additively coded genotype of a SNP with values 0, 1, or 2. Here, the interaction coefficient β_I is the estimand of G × E analysis. Hypothesis testing conducted on this coefficient provides evidence regarding the presence of G × E. Additionally, the magnitude of β_I quantifies the extent of G × E between SNP G_i and environment E_i on the phenotype Y_i.

2.1 | Statistical methods to detect single-variant G × E

We first examine the statistical model utilized for single-variant G × E analysis, which aims to identify specific genetic variants that exhibit variability across subgroups defined by the environmental exposures. This model has been extensively employed in the GWIS design.

2.2 | The basic model

For quantitative traits, a linear interaction model is typically used to model G × E, with the form

$$Y_i = \beta_0 + \beta_G G_i + \beta_E E_i + \beta_I G_i E_i + \epsilon_i$$

where the interaction coefficient β_I measures the G × E effects. Software such as plink (Purcell et al., 2007) and Regenie (Mbatchou et al., 2021), can be used to implement

computationally efficient GWIS, repeating the regression analysis for millions of SNPs in the genome.

For binary traits, several methods have been proposed to investigate G × E effects. One commonly used approach is implemented through logistic regression in case–control designs:

$$\text{logit}\left(\Pr\left(Y_i = 1 \mid G_i, E_i\right) = \beta_0 + \beta_G G_i + \beta_E E_i + \beta_I G_i E_i\right).$$

Testing the hypothesis $H_0: \beta_I = 0$ in this model assesses the presence of SNP × E interaction. However, it is recognized that this method has limited statistical power (Piegorsch et al., 1994). An alternative approach known as the case-only method has been developed (Piegorsch et al., 1994). This method relies on the assumption of independence between G_i and E_i in the underlying population. Essentially, under this assumption, the interaction test statistic in logistic regression becomes equivalent to testing the association between G_i and E_i among disease cases. In addition, under G–E independence, case-only analysis is known to be more efficient for estimating G × E compared with case–control analysis which is a more robust alternative not relying on G–E independence (Gauderman et al., 2017). However, the case-only method has a notable limitation: when the independence assumption is violated, it can lead to an inflated type-I error (Albert et al., 2001). Besides, directly testing the G–E independence assumption is challenging due to constraints in statistical power. To strike a balance between robustness and statistical power, empirical Bayes-type (EB) approaches have been introduced (Mukherjee & Chatterjee, 2008). The EB approach computes a weighted average of the case–control and case-only estimators of the G × E, exploiting a trade-off between bias and efficiency. The weights are estimated from the data by a stochastic framework to account for uncertainty in the assumption of G–E independence. A main advantage of this approach is that users can bypass the need to test the G–E independence assumption. Following this work, a more general method for deriving EB estimates has been proposed for all parameters of the general logistic regression model (Chen et al., 2009). A Bayesian model averaging framework has also been introduced to weight case–control and case-only estimates using posterior probabilities (Li & Conti, 2009). In conclusion, while logistic regression remains the most widely used method for case–control studies, alternative methods have been developed to improve efficiency under a range of weak or strong assumptions.

In the case of genome-wide G × E scans, several methods have been proposed to address various challenges. SPAGE provides a computationally efficient approach to deal with unbalanced case–control ratios (Bi et al., 2019). This approach fits a genotype-independent logistic regression model only once in the genome-wide analysis to reduce computational cost and uses saddle point approximation to calibrate the test statistics for binary outcomes with unbalanced case–control ratios. In addition, fastGWA-GE is a linear mixed model-based method for efficient and accurate genome-wide G × E analysis (Zhong et al., 2023). It controls for relatedness either through pedigree information or through a sparse genetic relationship matrix, and the effects of population stratification are captured using SNP-derived principal components.

2.3 | Two-step approaches and screening by vQTL

While the GWIS design enhances the replicability and robustness of G × E findings compared with candidate gene analysis, it also introduces a substantial burden of multiple testing, which significantly diminishes its statistical power (Aschard et al., 2012). Consequently, several "two-step" approaches have been proposed to improve the efficiency of G × E analysis while maintaining control over type I error. These approaches involve an initial step of SNP filtering, followed by testing for G × E using the selected SNPs at a modified significance level (Gauderman et al., 2017). Among the various two-step strategies, filtering by variance-associated genetic loci (vQTL) has recently been demonstrated to have higher effectiveness (Marderstein et al., 2021; Miao, Lin, et al., 2022).

A vQTL refers to a genetic locus that is associated with phenotypic variability. In the context of G × E analysis, we consider a linear model that incorporates the main effects of genetics and environments, as well as their interaction.

$$Y_i = \beta_0 + \beta_G G_i + \beta_E E_i + \beta_I G_i E_i + \epsilon_i, i = 1, \ldots, n,$$

where E_i is an environmental factor following a distribution F_E with mean μ_E and variance σ_E^2 (i.e., $E_i \sim F_E(\mu_E, \sigma_E^2)$), G_i is the additively coded genotype of a SNP with values 0, 1, or 2, and ϵ_i is the error term following a distribution $F_\epsilon((0, \sigma_\epsilon^2)$. We assume G_i, E_i, and ϵ_i to be mutually independent. Under this model, the conditional variance of Y_i given the genotype $G_i = g_i$ is

$$\mathrm{Var}[Y_i \mid G_i = g_i] = \sigma_\epsilon^2 + (\beta_E + \beta_I g_i)^2 \sigma_E^2,$$

This suggests that the conditional variance of Y_i may differ across genotype groups of G_i if the genetic variant is involved in interactions. Thus, a genetic variant showing SNP × E interaction is associated with the variance of the phenotype, that is, a vQTL, and one can use vQTL to screen for candidate SNP × E effects (Miao, Lin, et al., 2022).

Various statistical methods have been proposed to detect vQTLs, including classic non-parametric methods (Wang et al., 2019), full parametric methods (Young et al., 2018), and two-stage methods (Marderstein et al., 2021). However, these methods have certain limitations, such as a lack of robustness to non-Gaussian phenotypes and potential confounding effects on both trait levels and trait variability. To address these limitations, a recent method called QUAIL, a quantile regression-based framework, has been introduced (Miao, Lin, et al., 2022). In QUAIL, if a SNP G_i is a vQTL for trait Y_i, the conditional quantile function will exhibit different regression slopes (β_τ) for various quantile levels (τ):

$$Q_{Y_i}(\tau \mid G_i = g_i) = g_i \beta_\tau$$

QUAIL defined a quantile-integrated effect.

$$\beta_{QI} = \int_0^{0.5} (\beta_{\tau+0.5} - \beta_\tau) d\tau$$

which aggregates the differences between the regression coefficients of the upper and lower quantile levels (i.e., $\beta_{\tau+0.5-}\beta_{\tau}, \tau \in (0,0.5)$) across all quantile levels. The choice of 0.5 in $\tau + 0.5$ is to ensure that the quantile integral effect is equal to the difference of quantile-specific effect between all upper quantile levels ($\tau > 0.5$) and all lower quantile levels ($\tau < 0.5$). This quantile-integrated effect represents the magnitude of the vQTL effect of a SNP. Testing the vQTL effect of a SNP is equivalent to testing the null hypothesis $H_0: \beta_{QI} = 0$.

QUAIL estimates the quantile-integrated effect using various computational techniques to overcome the computational challenges associated with fitting standard quantile regression procedures that require iterative optimization for numerous quantile levels. It efficiently identifies vQTLs at the genome-wide scale, while overcoming the key limitations of traditional two-stage methods. Simulation studies have demonstrated that QUAIL exhibits greater power compared with other commonly used VQTL approaches when the phenotype is non-Gaussian distributed. In previous simulations, under a 0.4% phenotypic variance explained by G × E, QUAIL showed a 75% probability of rejecting the null hypothesis at a significance level of $P < 0.05$, while the best alternative methods had a 56% probability. When applied to UK Biobank data, QUAIL identified 11 novel vQTL for BMI (20% of the vQTL identified by all methods tested) compared with other methods (Miao, Lin, et al., 2022).

2.4 | Modeling multiple environments

The aforementioned approaches are primarily designed for G × E analysis of G × E with a single environmental variable. An alternative approach involves jointly modeling multiple environmental variables, which can potentially enhance statistical power by capturing a combination of variables that serve as proxies for the true underlying driver of interaction. Several methods have been proposed to accommodate the modeling of multiple environments simultaneously, such as StructLMM (Moore et al., 2019) and LEMMA (Kerin & Marchini, 2020). StructLMM is a computationally efficient method that aims to identify genetic variants interacting with one or more environments. It achieves this by modeling the environmental similarity between individuals across multiple environments as a random effect and testing G × E via the variance components test. On the other hand, LEMMA is a Bayesian whole-genome approach that allows for the joint modeling of SNP marginal effects and SNP G × E interaction effects with an environmental score (ES). The ES is a linear combination of multiple environmental variables and can be employed in single-variant-by-ES G × E inference. LEMMA employs variational inference techniques to fit the model, ensuring computational tractability even with large-scale datasets such as large biobanks. By incorporating multiple environmental variables and employing advanced modeling techniques, these approaches provide alternative strategies to enhance the analysis of G × E interactions beyond single environmental variable scenarios.

2.5 | Statistical method to detect polygenic G × E

Thus far, we primarily focused on interactions between a single genetic variant and the environment. However, it is now known that complex traits are influenced by numerous genetic variants scattered across the genome (Boyle et al., 2017). Therefore, contemporary G × E methods are increasingly emphasizing the investigation of how the polygenic

architecture of a trait varies across different environments. In the following sections, we will delve into several G × E methods that have been developed to leverage polygenicity by considering the G × E effects for all SNPs across the genome.

2.6 | Heritability and genetic correlation-based methods

This class of methods assesses whether the polygenic genetic basis of a trait varies across environments and typically examines the existence of any G × E (Bernabeu et al., 2021; Blokland et al., 2022; Martin et al., 2021). For demonstration, consider the trait under two different environments $E = 0$ and $E = 1$. We can express the trait values as follows:

$$Y^{(0)} = \sum_{j}^{M} G_j \beta_j^{(0)} + \epsilon^{(0)},$$

$$Y^{(1)} = \sum_{j}^{M} G_j \beta_j^{(1)} + \epsilon^{(1)},$$

Here, $Y^{(0)}$ and $Y^{(1)}$ represent the trait values in environments $E = 0$ and $E = 1$, and $\beta_j^{(0)}$ and $\beta_j^{(1)}$ denote the effect for jth SNP in environment $E = 0$ and $E = 1$, respectively. $\epsilon^{(0)}$ and $\epsilon^{(1)}$ represent the environment-specific noise terms.

Two common approaches are used to test for polygenic G × E effects: differential heritability and imperfect genetic correlation between environments. Based on the above model, we can define the environment-stratified heritability, which represents the proportion of phenotypic variance explained by SNPs, as follows:

$$h^{(0)^2} = \frac{\mathrm{Var}\left(\sum_j^M G_j \beta_j^{(0)}\right)}{\mathrm{Var}\left(Y^{(0)}\right)} \text{and} h^{(1)^2} = \frac{\mathrm{Var}\left(\sum_j^M G_j \beta_j^{(1)}\right)}{\mathrm{Var}\left(Y^{(1)}\right)}.$$

Testing for differential heritability is equivalent to testing the null hypothesis $H_0: h^{(0)^2} = h^{(1)^2}$. In contrast, the genetic correlation between the environments, can by written as

$$r_g = \frac{\mathrm{Cov}\left(\sum_j^M G_j \beta_j^{(0)}, \sum_j^M G_j \beta_j^{(1)}\right)}{\sqrt{\mathrm{Var}\left(\sum_j^M G_j \beta_j^{(0)}\right)\mathrm{Var}\left(\sum_j^M G_j \beta_j^{(1)}\right)}}$$

Testing for imperfect genetic correlation is equivalent to testing the null hypothesis $H_0: r_g = 1$. To perform statistical inference on these parameters, two types of methods are commonly used: the GREML-based approach (Yang et al., 2010) and linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015). Both methods aim to estimate environment-stratified heritability and genetic correlation across environments. GREML provides a more efficient estimator compared with LD score regression but requires

individual genotype and phenotype data as input. On the other hand, LD score regression, while less efficient than GREML, only requires environment-stratified GWAS summary statistics as input. Hypothesis testing based on these two approaches is often used to assess the existence of polygenic G × E.

Nevertheless, testing for differential heritability and imperfect genetic correlation may provide flawed results, if the goal is to examine the existence of G × E (Miao, Song, et al., 2022). For instance, heritability estimates may vary across discrete environments merely due to heteroscedasticity (i.e., differences in the residual variance components) in the absence of true G × E, leading to false positive G × E findings. Similarly, genetic correlation analysis between environments has its limitations. A perfect genetic correlation can be observed when the SNP additive effects are proportional between the environments, which is sometimes referred to as “amplification” in the G × E literature (Zhu et al., 2023). This leads to false negative results on testing G × E. Consequently, heritability and genetic correlation analyses are inadequate for proper estimation of polygenic G × E effects. Moreover, some of these approaches face technical challenges such as the inability to handle continuous environmental exposures.

2.7 | Variance component tests

Another class of methods directly assesses polygenic G × E using variance component tests. The G × E variance, which quantifies the extent to which phenotypic variation in a population is attributable to the interaction between genetic and environmental factors, serves as the target for estimation in these methods. Several approaches have been proposed to estimate G × E variance. One such approach is GCI-GREML, an extension of the GREML approach that focuses on estimating the proportion of phenotypic variance explained by G × E effects (Robinson et al., 2017). However, GCI-GREML assumes a homogeneous residual variance across environments, which may introduce bias in the results (Ni et al., 2019). To address this limitation, the MRNM approach was proposed as an extension of GCI-GREML (Ni et al., 2019). MRNM overcomes this limitation by considering both the genotype–environment correlation (which captures the association between genetic factors and environmental factors) and the residual–environment interaction (which captures the variation in non-genetic factors across different levels of environmental factors). However, MRNM cannot be used to model binary traits and only allows for univariate environments (Dahl et al., 2020). To address these issues, G × EMM was developed (Dahl et al., 2020). G × EMM is a mixed model framework analogous to GREML and is designed to capture the aggregate polygenic contributions of G × E effects. It can be applied to binary traits and general environments, allowing for a broader range of applications compared with MRNM. G × EMM estimates the heritability specific to each discrete environment or environmental extreme in the case of continuous environments.

Recent work suggests that to accurately assess the presence or absence of polygenic G × E, researchers should focus on estimating the G × E variance component, instead of differential heritability and imperfect genetic correlation analysis (Miao, Song, et al., 2022). However, current methods in the literature still have value in certain scenarios. For example, one study highlighted that differential heritability between environments may affect the predictive

accuracy of PGS in those environments, raising concerns about the universal applicability of PGS (Mostafavi et al., 2020). Imperfect genetic correlation analysis may be used to measure whether SNP effects are shared across environments (Bernabeu et al., 2021).

2.8 | Empirical PGS × E analysis

Another method, often referred as empirical PGS × E analysis, has become increasingly popular in the field of G × E research (Biroli et al., 2022; Domingue et al., 2020; Li et al., 2019; Schmitz et al., 2022). This approach involves a two-step procedure that begins by summarizing the genetic predisposition of each individual into a polygenic score (PGS). Subsequently, it examines the interaction between the PGS and the environment using a regression-based framework. The "empirical" in the title indicates the fact that PGS used in this type of analysis is not the true PGS, but a noisy estimate derived from an external GWAS.

A true PGS is typically defined as a weighted sum of effect alleles for a collection of SNPs $\mathrm{PGS}_i \sum_{j=1}^{M} G_{ij}\beta_{G_j}$, where the β_{Gj} are the true SNP effects for the jth SNP and G_{ij} indicates the number of copies of the effect alleles for the jth SNP (0, 1, or 2) for ith individual. Based on the true PGS, the data-generating model for PGS × E can be denoted as

$$Y_i = \alpha_{\mathrm{PGS}}\mathrm{PGS}_i + \alpha_E E_i + \alpha_I \mathrm{PGS}_i E_I + \epsilon_i,$$

where α_{PGS}, α_E, and α_I represents the main effects of the PGS PGS_i, environment E_i and the interaction between the PGS and environment, respectively. The estimand of PGS × E is α_I.

In practice, one can only use scores estimated from GWAS (denoted by empirical PGS $\widehat{\mathrm{PGS}_i}$) and perform empirical PGS × E analysis. For demonstration, we used the linear regression on quantitative traits as an example. The empirical PGS × E can be denoted as the following:

$$Y_i \sim \alpha_{\mathrm{PGS}}^{(\mathrm{Emp})}\widehat{\mathrm{PGS}_i} + \alpha_E^{(\mathrm{Emp})} E_i + \alpha_I^{(\mathrm{Emp})}\widehat{\mathrm{PGSE}_I},$$

where $\widehat{\mathrm{PGS}_i} = \mathrm{PGS}_i + s_i$, s_i is the estimation error in the PGS and $\mathrm{Cov}(\mathrm{PGS}_i, s_i) = 0$. The empirical PGS × E requires no overlap between the GWAS used to construct PGS and the sample for PGS × E analysis. Under this requirement, the hypothesis testing for empirical PGS × E, denoted as $H_0: \alpha_I^{(\mathrm{Emp})} = 0$ is equivalent to the hypothesis testing for PGS × E, $H_0: \alpha_I = 0$. However, this point estimation is substantially affected by the imprecision in PGS estimation due to limited sample sizes in GWAS. Neglecting the inherent uncertainty in the empirical PGS can lead to interaction estimates that are biased toward zero (i.e., $\left|E\left[\widehat{\alpha}_I^{(\mathrm{Emp})}\right]\right| < |\alpha_I|$. In cases where sample overlap exists between the GWAS and the PGS × E analysis, PGS will overfit the data, resulting in biased estimates of interaction and potential false discoveries in empirical PGS × E analysis (Miao, Song, et al., 2022).

The PGS × E approaches mentioned previously are based on linear regression for quantitative traits. For binary traits, the model for PGS × E analysis can be formulated by replacing the single variant in the logistic regression-based G × E analysis with the true PGS. Case-only methods have also been proposed for PGS × E analysis (Meisner

et al., 2019). These methods exploit the G–E independence to enhance the power of logistic regression-based tests. In addition, a recent method simultaneously models G–E correlations and G × E using PGS in case–control studies (Wang et al., 2023). It uses a logistic-normal regression framework to quantify both disease risk and the PGS distribution in the population, and proposes joint inference using the retrospective likelihood of case–control data.

2.9 | PIGEON

A key issue for all these aforementioned methods for polygenic G × E inference is, although all these approaches are referred to as G × E analysis in the literature, the relationship between these approaches is poorly understood. For example, it is unclear whether PGS × E and differential heritability analysis aim to estimate the same parameter. Consequently, a consistent language to describe the connections and distinctions among these methods is lacking. There is a pressing need for a comprehensive framework for quantifying polygenic G × E.

To bridge this gap, (Miao, Song, et al., 2022) proposed PIGEON, a unified statistical framework designed for estimating polygenic G × E. PIGEON is constructed based on a linear mixed model that captures both the additive effects and G × E effects for many SNPs.

$$Y_i = \sum_{j=1}^{M} G_{ij}\beta_{G_j} + E_i\beta_E + \sum_{j=1}^{M} G_{ij}E_i\beta_{I_j} + \epsilon_{i0} + \epsilon_{i1}E_i .$$

Here, Y_i is the standardized phenotype with a mean of 0 and variance of 1 for the ith individual, G_{ij} is the jth standardized SNP, E_i is the standardized environment, ϵ_{i0} is the noise term, and $\epsilon_{i1}E$ quantifies the heteroskedasticity arising from the interaction between the residual variance and the environment (i.e., the variation in residual variance across different environments). Polygenic additive effects and interaction effects (i.e., β_{G_j} and β_{I_j}) are modeled as random variables.

In the PIGEON framework, two main objectives are defined for G × E inference: G × E variance and covariant G × E. These two objectives aim to quantify the overall contribution of G × E to the phenotype and provide mechanistic insights into the interaction mechanisms, respectively. The G × E variance is a measure of the overall G × E contribution and is defined as the variance of the interaction effects, represented as $\sigma_I^2 = \mathrm{Var}(\beta_{I_j})$, where M is the total number of SNPs. Hypothesis testing on this quantity helps determine the evidence of any G × E. The magnitude of the G × E variance component quantifies the extent of G × E for the trait of interest. This is similar to the variance component tests we have introduced above. However, solely having a non-zero G × E variance does not provide detailed mechanistic insights into the interactions. To gain a deeper understanding of the polygenic G × E, PIGEON introduces the concept of covariant G × E, that is, $\rho_{GI} = \mathrm{Cov}(\beta_{G_j}, \beta_{I_j})$. This measure captures the covariance between SNP additive effects (ρ_{GI}) and SNP × E interaction effects (β_{I_j}) across the genome. By examining the correlation between the effects of SNPs on

complex traits and their tendency to interact with the environment, the covariant G × E offers valuable insights into the underlying interaction mechanisms at a whole-genome level.

The two major objectives in the PIGEON framework serve as the foundation for quantifying evidence of polygenic G × E and interpreting the underlying mechanisms of these interactions. PIGEON also establishes the connections between existing G × E approaches, allowing us to understand their relationships, distinctions, and limitations. The objectives of differential heritability and imperfect genetic correlation are associated with the G × E variance which primarily focuses on providing evidence for the presence of polygenic G × E. On the other hand, PGS × E analysis is linked to the covariant G × E objective, which aims to interpret the mechanisms underlying polygenic G × E.

As mentioned in the section above, empirical PGS × E analysis is substantially affected by the imprecision in PGS estimation due to limited sample sizes in GWAS. Ignoring the uncertainty in empirical PGS leads to biases toward zero in the interaction coefficient estimates. In contrast, Importantly, PIGEON reveals a direct relationship between the coefficients of the oracle PGS × E analysis (which is based on the true PGS and described in “Empirical PGS × E analysis” section above) denoted as a_I from and the covariant G × E represented by ρ_{GI}

$$\alpha_I = \frac{\rho_{GI}}{\sigma^2_G},$$

where σ^2_G is the additive heritability of the outcome of interest. The oracle PGS × E represents an upper bound and infinite sample limit of empirical PGS × E, analogous to heritability being the upper bound of PGS predictive R^2 in the GWAS literature. Therefore, as a superior alternative to commonly used PGS × E analysis, estimating covariant G × E through variance component analysis provides a more reliable approach to quantifying and interpreting polygenic G × E effects.

PIGEON also introduces an estimation strategy called PIGEON LDSC which allows for the estimation of polygenic G × E effects using only GWIS and GWAS summary statistics as the input. It is unbiased, computationally efficient, and robust to sample overlap, heteroscedasticity, and gene–environment correlation. Two methods can be used to estimate the G × E variance component: PIGEON and G×Esum (Shin & Lee, 2021). Both methods utilizes the Z-scores for SNP × E interaction effects obtained from GWIS summary statistics. The PIGEON LDSC method calculates the expected value of the squared Z-score for each SNP × E interaction effect, denoted as z_{Ij}. Regressing the squared Z-scores on the LD score provides the estimator of the G × E variance component accurately:

$$\mathbb{E}\left[z^2_{Ij} \mid \ell_j\right] = \frac{N_I \sigma^2_I}{C^2 M}\ell_j + \left[1 + (\mu_E(4) - 1)\left(\sigma^2_G + \sigma^2_{\epsilon_1}\right)\right]/C^2,$$

where N_I denotes the GWIS sample size, σ_I^2 is the G × E variance component, M is the number of SNPs, $C = \sqrt{1 - \frac{Z_E^2}{Z_E^2 + N_I - 2}}$ is a correction factor to account for the environmental effect on Z-score approximation in GWIS, Z_E^2 is the Z-score of environmental effect, ℓ_j is the LD score, and $\mu_E(4)$ is the kurtosis of the environment.

To estimate covariant G × E, PIGEON LDSC only requires GWIS and GWAS summary statistics with arbitrary sample overlap. The expected value of the product of additive effect Z-scores and SNP × E effect Z-scores is

$$\mathbb{E}\left[z_{G_j} z_{I_j} \mid \ell_j\right] = \frac{\sqrt{N_G N_I}\rho_{GI}}{CM}\ell_j + \frac{N_s}{C\sqrt{N_G N_I}}\left(2\rho_{GI} + \beta_E^2 \mu_E(3)\right),$$

where ρ_{GI} is the covariant G × E, M is the number of SNPs, $C = \sqrt{1 - \frac{Z_E^2}{Z_E^2 + N_I - 2}}$ is a correction factor described above, Z_E^2 is the Z-score of environment effects, ℓ_j is the LD score, N_I and N_G represents the GWIS and GWAS sample size, N_s is the number of overlapped samples between GWIS and GWAS analysis, $\mu_E(3)$ is the skewness of the environment. The oracle PGS × E coefficient can be obtained by normalizing the covariant G × E by heritability.

With this approach, it has become possible to only use GWIS and GWAS summary statistics to perform G × E inference, especially PGS × E analysis. The most important feature is its robustness to sample overlap. In traditional G × E approaches, the presence of shared samples between GWAS and G × E cohorts renders PGS generation and subsequent PGS × E analysis impossible, due to the concern of inflated type-I error. With PIGEON, unbiased estimates for covariant G × E and oracle PGS × E can now be obtained, regardless of sample overlap. Another advantage of PIGEON is its ability to facilitate hypothesis-free scans for PGS × E. Unlike most studies that define PGS based on the same outcome used in G × E analysis, PIGEON offers a superior strategy. It allows researchers to perform GWIS in large samples through meta-analysis and then examine its genetic correlation with multiple published GWAS. This strategy eliminates the concerns regarding whether the GWAS and GWIS were conducted on the same or distinct samples, allowing for a comprehensive assessment of PGS × E effects across multiple PGS.

2.10 | Gene–environment correlation in G × E research

The environments in many G × E applications can be partially endogenous, creating complex patterns of gene–environment correlations (rGE) that pose inferential challenges for identifying G × E (Jaffee & Price, 2007). In many applications of G × E, it is of great interest to ensure the exogeneity of E (Barcellos et al., 2018; Schmitz & Conley, 2017; Zhu et al., 2023). When G × E analysis is performed on observational data, some studies go to great lengths to use instrumental variables or other approaches (Barcellos et al., 2018; Schmitz & Conley, 2017). Some studies focus on the interaction between SNPs in autosomes and sex (Blokland et al., 2022; Zhu et al., 2023), while other studies ignore the potential correlation between genes and environment (Robinson et al., 2017).

For single-variant G × E analysis, the rGE can lead to spurious G × E results (Dudbridge & Fletcher, 2014). Sensitivity analyses have been suggested to reduce the possibility of false-positive reports of interaction (Dudbridge & Fletcher, 2014). For polygenic G × E analysis, a much weaker condition than G–E independence, that is, zero correlation between additive SNP effects on environment and SNP × E effects on outcome, is sufficient to obtain unbiased estimates and well-controlled false-positive rates in polygenic G × E inference (Miao, Song, et al., 2022). If this weak condition is violated, a solution is also proposed to correct for biases introduced by rGE (Miao, Song, et al., 2022). In conclusion, it is important to recognize the impact of rGE on G × E inference and to select appropriate statistical methods and sensitivity analyses to reduce false-positive findings.

3 | CONCLUSION

Despite the long-standing interest in G × E, our understanding of its contribution to human complex traits and diseases remains limited. The study of G × E interactions presents statistical challenges due to the high dimensionality of genetic information and environmental exposures, the need for large sample sizes to reliably detect G × E effects, and the scarcity of large datasets that combine genetic and environmental data. In this article, we aim to review the current state-of-the-art statistical methods on G × E inference. We discussed two main categories of methods designed for single-variant analysis and polygenic G × E analysis. These approaches represent a tradeoff between statistical power and resolution of findings. Single-variant analysis, while having lower power, offers higher resolution, making it valuable for identifying specific genetic variants involved in G × E interactions. In contrast, polygenic G × E analysis, with its higher power but lower resolution, aims to leverage genome-wide information to provide an understanding of the collective contribution and interpretation of G × E effects across all SNPs. These methods have laid the foundation for identifying and interpreting robust G × E interactions and hold significant potential for broad applications in many disciplines.

There are several important directions for future G × E methodological research. Firstly, the remarkable success of complex trait genetics, particularly through large-scale GWAS meta-analyses and the sharing of summary association statistics, has revolutionized how we approach genotype–phenotype associations. In contrast, G × E analysis still predominantly relies on small cohorts with individual-level genetic, exposure, and outcome data to date. To propel the field forward, it is crucial to meta-analyze and widely share GWIS summary statistics. Future developments in G × E methodology should prioritize approaches that leverage summary-level data, enabling more extensive collaboration and data integration efforts. Secondly, a lingering challenge is accurately quantifying the overall contribution of G × E across all relevant environments. The current G × E studies rely on single or several hypothesized environmental exposures. Understanding the cumulative impact of G × E across all possible environments remains an open question. Thirdly, unraveling the functional interpretation of G × E interactions presents another intriguing challenge. Identifying the underlying mechanisms and biological pathways through which genes and environmental factors interact to influence complex traits is essential for gaining deeper insights. Future research should strive to develop innovative methodologies that integrate genetic, environmental, and functional genomic data to elucidate the functional implications

of G × E interactions. Fourth, the current gold-standard of PGS × E analysis involves performing regression within families, which effectively eliminates all bias from population stratification, environmental confounding, assortative mating, and other sources (Biroli et al., 2022). It is an open question whether the methods discussed might have biases for the reasons mentioned above when applied to population-level data, and if so, whether they can be used for within-family analyses. Fifth, it is important to recognize that the statistical methods discussed in this review all focus on G × E analyses using molecular genetic data. Before the advent of molecular genetic data made possible by advances in sequencing technologies, researchers used twin- and family-based analyses to study G × E (Dick, 2011). These methods relied on latent, unobserved indices of genetic influence to detect the presence of G × E. An example from twin studies is the analysis of monozygotic twins raised apart, which examines the effect of different environments on some traits with identical genotypes (Bergeman et al., 1988). Another example is differential heritability analysis, which compares twin-based heritability across different environments (Turkheimer et al., 2003). A valuable avenue for future research would be to compare the results and models from twin- and family-based studies with those from molecular analyses in the context of G × E to better understand the strengths and limitations of each study design.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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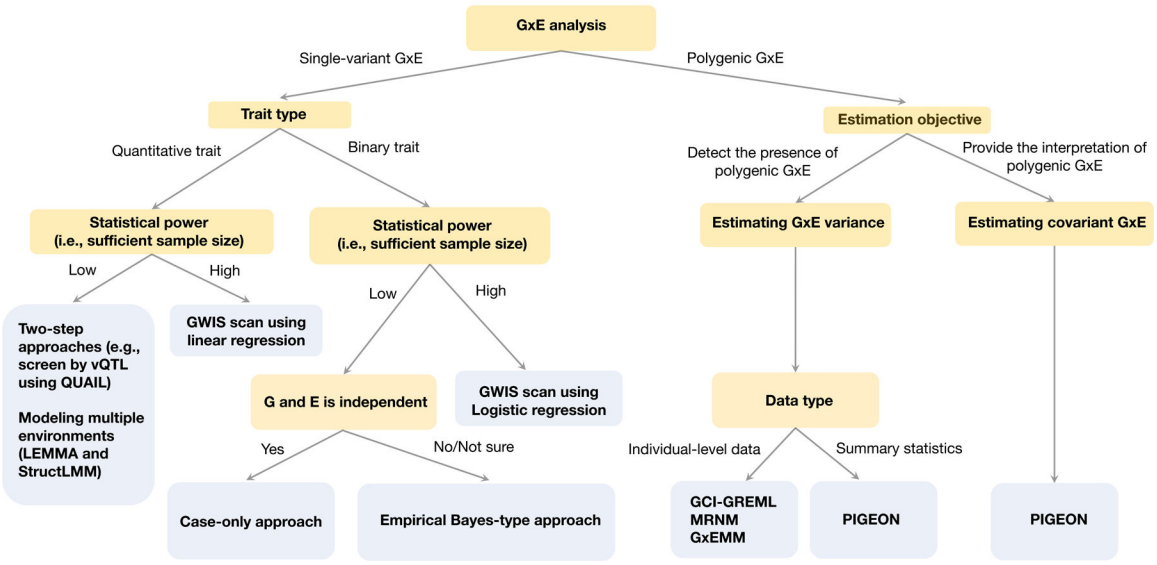

FIGURE 1.

A decision tree for guiding the selection of appropriate methods for G × E inference. The decision node, depicted by the yellow block, serves as the starting point for determining the suitable approach. The blue blocks represent the specific methods to be employed based on the decision made at the decision node.

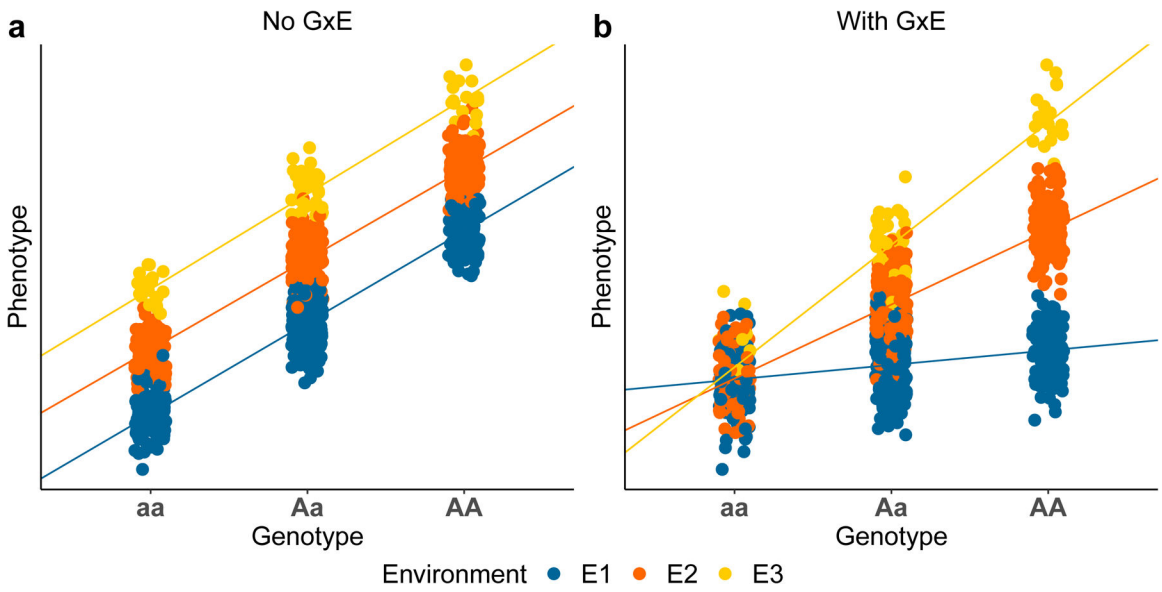

FIGURE 2.

An illustration of G × E. Each data point represents an individual, where the *X*-axis denotes the genotype, and the *Y*-axis represents the phenotype value. Three different colors indicate three distinct environments. (a) In the absence of G × E, the genetic effect on the phenotype remains consistent across all three environments, as depicted by the fitted line parallel to each other. (b) In the presence of G × E, the genetic effect on the phenotype varies across the three environments. The largest effect is observed in the environment highlighted in yellow. This variation is illustrated by the fitted lines not being parallel to each other, indicating that the relationship between genotype and phenotype depends on the environment.

TABLE 1

Software tools for G × E methods reviewed in this article.

Category	Methods	Study design	Software
Single-variant G × E	Linear regression	Cohort study	https://www.cog-genomics.org/plink/2.0/assoc#glm
	Logistic regression	Cohort and case–control study	https://www.cog-genomics.org/plink/2.0/assoc#glm
	Case-only approach	Cohort, case-only, and case–control study	https://bioconductor.org/packages/release/bioc/html/CGEN.html
	Empirical Bayes-type approach	Cohort and case–control study	https://bioconductor.org/packages/release/bioc/html/CGEN.html
	QUAIL	Cohort study	https://github.com/qlu-lab/QUAIL
	LEMMA	Cohort and case–control study	https://github.com/mkerin/LEMMA
	StructLMM	Cohort and case–control study	https://github.com/limix/struct-lmm
	GCI-GREML	Cohort and case–control study	https://bio.tools/mtg2
	SPAGE	Cohort and case–control study	https://github.com/WenjianBI/SPAGE
	fastGWA-GE	Cohort and case–control study	https://yanglab.westlake.edu.cn/software/gcta/#fastGWA-GE
Polygenic G × E	MRNM	Cohort and case–control study	https://bio.tools/mtg2
	G × EMM	Cohort and case–control study	https://github.com/andywdahl/gxemm
	PIGEON	GWIS summary statistics from cohort and case–control study	https://github.com/qlu-lab/PIGEON