REVIEW ARTICLE

# Dimensional and transdiagnostic phenotypes in psychiatric genome-wide association studies

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Genome-wide association studies (GWAS) provide biological insights into disease onset and progression and have potential to produce clinically useful biomarkers. A growing body of GWAS focuses on quantitative and transdiagnostic phenotypic targets, such as symptom severity or biological markers, to enhance gene discovery and the translational utility of genetic findings. The current review discusses such phenotypic approaches in GWAS across major psychiatric disorders. We identify themes and recommendations that emerge from the literature to date, including issues of sample size, reliability, convergent validity, sources of phenotypic information, phenotypes based on biological and behavioral markers such as neuroimaging and chronotype, and longitudinal phenotypes. We also discuss insights from multi-trait methods such as genomic structural equation modelling. These provide insight into how hierarchical 'splitting' and 'lumping' approaches can be applied to both diagnostic and dimensional phenotypes to model clinical heterogeneity and comorbidity. Overall, dimensional and transdiagnostic phenotypes have enhanced gene discovery in many psychiatric conditions and promises to yield fruitful GWAS targets in the years to come.

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## DIMENSIONAL AND TRANSDIAGNOSTIC PHENOTYPES IN PSYCHIATRIC GENOME-WIDE ASSOCIATION STUDIES

The field of molecular psychiatric genetics has made enormous advances in the last decade, predominantly through large-scale case-control genome-wide association studies (GWAS) [1–7]. GWAS have catalyzed genetic discovery by identifying hundreds of replicable molecular genetic markers associated with mental health conditions. The findings provide insights into the molecular basis of complex traits, downstream biological processes, and genetic architecture of psychiatric conditions. Summary statistics from GWAS allow for the estimation of genetic correlations among an array of traits and disorders and the calculation of polygenic scores (PGS), which enable the investigation of the correlates and sequelae of genetic risk.

Most of the progress to date has been achieved using GWAS dependent on binary, case-versus-control analyses embedded within traditional diagnostic classification systems. Obtaining large sample sizes is critical to increasing GWAS power, and a case-control design is well-suited for attaining and mega-analyzing large samples from electronic medical records, direct-to-consumer genetic testing, and other sources. As effective as this approach has been, the single nucleotide polymorphisms (SNPs) identified by the most recent diagnostic GWAS explain relatively little of the heritability of psychopathology (e.g., approximately 8% for major depressive disorder (MDD) [8] and 24% for schizophrenia [9]). One approach to discovering unique genetic variants associated with psychopathology has focused on incorporating novel phenotypes. Quantitative and transdiagnostic approaches to phenotype measurement—including but not limited to symptom severity; personality and behavioral traits; clinical features such as age-at-onset and recurrence; ecological momentary and ambulatory assessments utilizing surveys; actigraphy and smartphone sensing; and laboratory-based markers from blood tests and neuroimaging—can complement insights gained from case-control GWAS to enhance power for gene discovery.

The current review focuses on recent developments in dimensional, transdiagnostic, and other novel phenotypic

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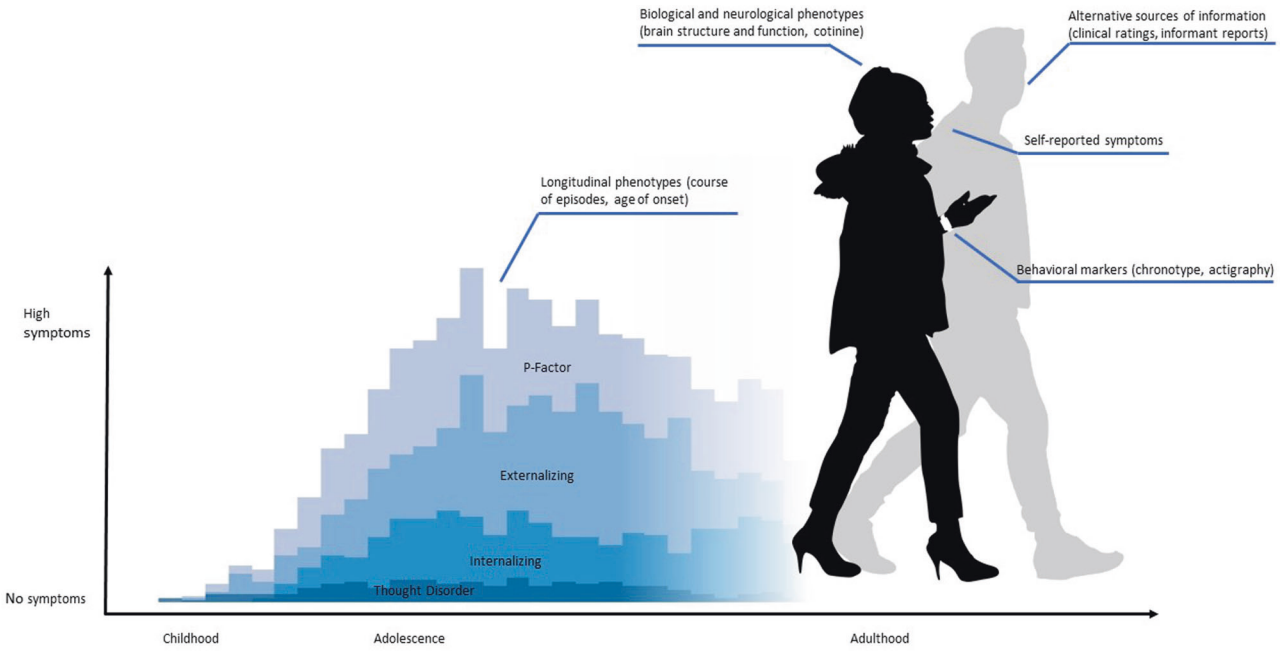


**Fig. 1 Dimensional and transdiagnostic GWAS phenotypes across the lifespan.** Psychiatric phenotypes demonstrate temporal features such as age of onset and developmental trajectories, 'state' fluctuations around the 'stable' severity levels, recurrences, and treatment response. Many dimensional, transdiagnostic, and other non-diagnostic phenotypes are well-suited to measuring such temporal features. Higher-order phenotypes such as the general factor of psychopathology (p-factor) can 'lump' symptom burden at a particular point in time. The most optimal sources of information may vary across the lifespan, e.g., externalizing behaviors might be assessed via informant-reports in childhood, and via self-reports and cotinine in adulthood.

definitions in GWAS across all major psychiatric and neurodevelopmental disorders. We identify a number of useful properties of quantitative phenotypes, including the impact of such phenotypes on statistical power and validity, the utility of illness course, informant report, and behavioral and biological phenotypes, and the potential of hierarchical 'splitting' and 'lumping' approaches (Fig. 1). Our goal is to appraise this evolving literature in psychiatric GWAS, synthesize its accomplishments to date, and identify avenues for future research.

## THEMES IN DIMENSIONAL AND TRANSDIAGNOSTIC GWAS

### Sample size

Gene discovery necessitates large samples, as sample size is one of the most important factors determining statistical power in GWAS. Since phenotype operationalization can limit sample size—expensive or time-consuming phenotypes being harder to collect on large samples—phenotype operationalization can thereby influence statistical power for gene discovery [10, 11]. This issue applies to both case-control (e.g., diagnostic) and non-diagnostic dimensional phenotypes, as either can be operationalized in such a way as to maximize sample size. While the prototypical diagnostic GWAS uses structured interviews administered by trained clinicians, diagnoses abstracted from electronic medical records yield large sample sizes and have demonstrated utility as target phenotypes [12, 13]. However, some diagnoses have been shown to be underrepresented in electronic medical records [14], and optimal clinical diagnoses require trained clinicians and lengthy interviews. Conversely, a comprehensive dimensional measure of psychopathology can be collected in under one hour [15–17]. Computer-adaptive methods that select the most appropriate items for each individual can further reduce length [18]. While some quantitative phenotypes are costly—for example, imaging phenotypes collected by the ENIGMA consortium ($N = 30{,}000$–$50{,}000$) [19, 20]—many quantitative phenotypes, particularly those evaluating symptoms and behaviors, are inexpensive to collect—for instance, self-reported well-being ($N = 298{,}420$) [21]. Ascertaining large, representative samples is challenging, regardless of phenotype. However, for a given amount of money, time, and other resources, a carefully-designed quantitative phenotype may allow for a larger sample than a case-control design. In sum, operationalizing phenotypes so as to maximize sample size may improve statistical power for gene discovery, assuming phenotypes are equally reliable and valid, assumptions we discuss below.

### RELIABILITY

Reliability is a function of how closely scores on a measure match individuals' true standing on the underlying trait. In GWAS, this underlying trait is genetic risk. According to the common-disease common-variant framework [22], genetic risk is attributable to many small effects, which in aggregate approximate a normal distribution [23]. If genetic risk is continuously distributed, measures that most reliably assess individuals' standing on that continuum should maximize power for gene discovery. In all statistical association tests, dichotomizing a continuous variable decreases statistical power [24, 25]. When a continuous trait is dichotomized at the median, the loss of statistical power is equivalent to discarding a third of the sample—the loss increases as the cut-point moves away from the median [24]. In their 2010 analysis, Yang, Wray, and Visscher extended findings on the effects of dichotomization to simulated GWAS [26]. Yang and colleagues show that for a given sample size drawn from a population-based sample, a quantitative trait will always outperform a case-control phenotype in terms of power, as information is always lost when the continuous trait is transformed to be binary. This is because the case-control dichotomization discards information about severity: an individual with persistent, severe symptoms is made statistically equivalent to an individual with mild symptoms that barely surpass the diagnostic threshold. As an example, the interrater reliability of dimensional measures of

positive and negative symptoms of schizophrenia ranges from 0.70 to 0.92 [27], whereas the interrater reliability of schizophrenia in DSM-5 field trails was 0.50 [28]. Similarly, interrater reliability for the Hamilton Rating Scale for Depression averages 0.94 [29], whereas that of MDD diagnosis is only 0.28 [28]. Accordingly, dichotomizing questionnaire data into the most and least severe scores, without including variability in the middle range, has also been shown to reduce GWAS power. Moreover, poor reliability results in diagnostic misclassifications, which decrease heritability and inflate genetic correlations between diagnoses [30].

Empirical studies corroborate the conclusions from simulations, showing that quantitative phenotypes detect more, and more novel, SNPs, than case-control phenotypes. Dimensional phenotypes identified additional novel significant loci compared with diagnostic phenotypes in the two largest PTSD GWAS [31, 32]. Whereas case-control PTSD GWAS ($N = 214{,}408$) uncovered three loci, fifteen loci were identified using dimensional PTSD phenotypes ($N = 186{,}689$), even with a smaller sample [31]. Despite high genetic correlations among dimensional, diagnostic, and external PTSD phenotypes, only one of the fifteen loci identified in the dimensional GWAS was also identified in the case-control GWAS, indicating the dimensional phenotype provided unique information. Likewise, a recent case-control GWAS of self-reported anxiety diagnosis yielded two significant SNPs ($N = 224{,}330$), whereas a dimensional anxiety severity phenotype based on a two-item instrument in a slightly smaller sample size ($N = 199{,}611$) yielded four additional SNPs [33]. Overall, GWAS of dimensional phenotypes have been fruitful, collectively revealing hundreds of novel SNPs associated with psychiatric disorders.

The impact of phenotype definition on SNP-based heritability is less clear. Case-control phenotypes have occasionally resulted in higher SNP-based heritability estimates. In a depression GWAS, a diagnosis phenotype had an estimated $h_{SNP} = 0.113$, self-reported diagnosis phenotype had $h_{SNP} = 0.078$, and dimensional depression severity phenotype had $h_{SNP} = 0.055$ [34]. Larger heritability estimates for case-control phenotypes relative to dimensional phenotypes are consistent with other depression GWAS [8, 35] as well as anxiety disorders GWAS [33]. Jermy and colleagues (2021) showed a dimensional phenotype calculated from fifteen symptoms of depression increased the SNP-based heritability by 1.4%, on average, relative to a dichotomous phenotype based only on cardinal symptoms, although a number of quantitative phenotypes did not markedly improve SNP-based heritability [36]. Many of these GWAS had similar sample sizes for dimensional and diagnostic phenotypes, hence these potential differences do not appear to be artifacts of discovery N.

It is important to note that most of studies cited above were based on population samples. For rare phenotypes—i.e., severe psychosis—oversampling for the pathological end of the dimension can increase the power of case-control designs [26]. However, little is known about how oversampling affects GWAS of dimensional phenotypes. If, for example, the sum of ratings on the Young Mania Rating Scale [37] were used instead of DSM-defined bipolar disorder, oversampling for bipolar disorder cases might also increase quantitative GWAS power in a way that is not accounted for in the simulations reported in Yang, Wray, and Visscher (2010).

## CONVERGENT VALIDITY

Dimensional phenotype GWAS often have strong genetic correlations with case-control GWAS of the same construct, implying convergent validity between the two. A recent study used three depression phenotypes in GWAS of comparable sample sizes: an ICD code-based algorithm derived from electronic health records, a self-reported physician diagnosis, and a dimensional symptom scale [34]. Genetic correlations among these three definitions were high ($r_g > 0.88$). In the two largest PTSD GWAS to date, genetic correlations between dimensional and case-control (diagnostic) phenotypic definitions were very strong, nearing 1.00 [31, 32].

The data from substance use disorders similarly indicates convergent validity between dimensional and case-control phenotypes. Self-reported problematic alcohol use is moderately genetically correlated with alcohol dependence ($r_g = 0.63$) [38]. The degree to which dimensional phenotypes align with case-control phenotypes is likely moderated by the source of information (see section: Source of Information). The close correlation between alcohol use and alcohol dependence might be in part due to the data for both phenotypes being most often derived from an individual's self-report.

Table 1 reports genetic correlations between selected corresponding dimensional and diagnostic phenotypes of comparable sample size, to illustrate convergent validity—moderate to high correlations between different measures of conceptually similar phenotypes—and discriminant validity—low correlations between measures of conceptually distinct phenotypes. In general, correlations between similar phenotypes are moderate to very strong. The genetic correlation between a dimensional measure of PTSD symptoms [31] and a PTSD diagnosis [39] ($r_g = 0.92$) is very strong, and the correlation between a dimensional measure of problematic alcohol use [38] and alcohol use disorder [40] ($r_g = 0.71$) is strong, in line with published

**Table 1.** Genetic correlations ($r_g$) between dimensional and categorical phenotype.

| | | **Categorical phenotype** | | | |
|---|---|---|---|---|---|
| **Dimensional phenotype** | **GWAS N** | **PTSD dx [39] 174,659** | **GAD dx [115] 58,133** | **MDD dx [42] 510,321** | **AUD dx [40] 267,080** |
| 1. PTSD sx on PCL total [31] | 186,689 | **0.92 [0.75, 1.00]** | 0.57 [0.85, 0.99] | 0.64 [0.59, 0.69] | 0.34 [0.27, 0.41] |
| 2. GAD sx on GAD-2 [33] | 175,163 | 0.95 [0.77, 1.00] | **0.59 [0.49, 0.68]** | 0.66 [0.60, 0.72] | 0.37 [0.27, 0.47] |
| 3. Neuroticism [41] | 170,911 | 0.60 [0.46, 0.74] | 0.69 [0.63, 0.74] | **0.68 [0.65, 0.71]** | 0.24 [0.17, 0.30] |
| 4. AUD sx on AUDIT-P [38] | 121,568 | 0.40 [0.23, 0.57] | 0.29 [0.18, 0.30] | 0.29 [0.21, 0.36] | **0.71 [0.62, 0.80]** |

*Sx* Symptom dimensions, *dx* Diagnosis, *PCL* Post-traumatic stress disorder checklist, *GAD-2* Generalized anxiety disorder 2-item, *AUDIT-P* Alcohol use disorders identification test, problems subscale, *PTSD* Post-traumatic stress disorder, *GAD* Generalized anxiety disorder, *MDD* Major depressive disorder, *AUD* Alcohol use disorder.

All genetic correlations and heritability estimates were calculated using LD score regression (LDSC version 1.0.1 [149]), with LD scores computed from European ancestry individuals from the 1000 Genomes study. Summary statistics are based on GWAS of European-ancestry cohorts. Genetic correlations between diagnostic and dimensional phenotypes of corresponding phenotypes are bolded.

Corresponding dimensional and categorical phenotypes are based on summary statistics from discovery samples of comparable size.

Note that the GAD-2 is a 2-item measure of anxiety, illustrating the limitations of this and other "minimal phenotypes", as this measure has significant genetic correlations with a number of phenotypes capturing non-specific genetic risk.

findings. This pattern holds even between a higher-order dimensional phenotype, such as neuroticism [41], and a specific diagnosis such as MDD [42] ($r_g$=0.68; see the section on "Lumping and Splitting" for discussion of higher-order phenotypes). Some diagnoses and symptoms that do not correspond directly are very strongly correlated, e.g. $r_g = 0.95$ between PTSD [39] and symptoms of anxiety [33], which reflect the expected pleiotropy, as well as the heterogeneity of diagnoses and limitations of "minimal phenotypes".

In some cases, non-diagnostic phenotypes have shown poor convergence with case-control phenotypes. First, a GWAS of "minimal phenotypes" of depression, i.e. assessments comprising just a few items, was critiqued as identifying non-specific loci [43, 44]. However, it is important to distinguish between phenotype conceptualization and phenotype operationalization. Reliability is determined by phenotype operationalization, which places an upper limit on validity. Minimal phenotypes—whether dimensional, such as a few items assessing depression, or dichotomous, such as self-reported diagnosis or diagnoses obtained from electronic medical records—are likely to be less reliable, and the resulting GWAS will have lower specificity, and consequently lower validity. Second, initial GWAS of a subset of items from the alcohol use disorders Identification Test (AUDIT) [45] measuring alcohol consumption had only low to moderate convergence with alcohol use disorder [40]. Subsequent item-level modeling revealed that one item captured socially-stratified differences in alcohol use behavior rather than the alcohol phenotypes of clinical interest [46]. GWAS using an empirically-derived consumption score found high convergence with alcohol use disorder [46], indicating that scale psychometrics may change when investigated at the genetic level, necessitating revised scoring for GWAS.

Third, GWAS of self-reported psychosis-like experiences in adolescents, positive symptoms, cognitive problems, and both self- and parent-reported negative symptoms resulted in small genetic correlations with schizophrenia [47]. Some domains of psychosis-like experiences were negatively correlated with bipolar disorder, in contrast to the strong positive genetic correlations observed between the schizophrenia and bipolar disorder diagnostic GWAS [48]. In this case, weak genetic correlations may be attributable to partially differential genetic liabilities underlying psychopathology across development (see "Longitudinal Phenotypes", below), as well as imperfect phenotypic correspondence between individual symptom dimensions and heterogeneous diagnoses. For example, the schizophrenia diagnosis comprises several major symptom dimensions, including reality distortion, unusual psychosis-like experiences, dissociation, anhedonia, and emotional detachment [49], hence the genetic liability for a single symptom domain will only partially overlap with genetic risk for the diagnostic category.

## SOURCE OF INFORMATION

Quantitative and transdiagnostic phenotypes can reflect information from an array of sources, including friends, significant others, parents, teachers, and most commonly, self-report. A common concern about such phenotypes is that some clinical phenomena may not be accurately measured via self-report. The differences between self-reported and clinician-rated psychopathology, and their implications for gene discovery, is a topic requiring more research. In some disorders, such as psychotic disorders, lack of insight is common, and interviewer-rated symptoms may capture psychopathology that self-reports do not. In a population sample, however, a GWAS of self-reported psychotic experiences identified two genome-wide significant associations [50]. Genetic correlation analysis identified significant genetic correlations between psychotic experiences and MDD ($r_g = 0.46$), autism spectrum disorder ($r_g = 0.39$), ADHD ($r_g = 0.24$), and schizophrenia ($r_g = 0.21$), and a PGS for self-reported psychotic symptoms was associated with development of psychosis in a longitudinal cohort. The sparse self-report data may explain non-specific associations between self-reported psychotic symptoms and psychiatric disorders. Results may also be affected by excluding individuals with psychotic disorders from the analysis. Regardless, these results suggest the GWAS of self-reported psychotic experiences identified novel loci with some relevance to psychopathology broadly, and perhaps psychosis specifically. This hints at the potential of self-reported symptoms to capture the same genetic vulnerability to psychopathology as diagnostic data.

In some cases, self-report may be more valid than informant report. Pain et al. (2018) showed that self-reported anhedonia was more heritable than parent-rated negative symptoms[47], and self-reported internalizing symptoms were more heritable than informant-reported symptoms [51]. This may be because internal mood states are generally considered more amenable to self-report than informant report [52, 53]. Similarly, psychopathology and traits that are highly stigmatized, unlawful, taboo, or that may not be readily observable—e.g. theft—are more amenable to self-report than informant-report [54, 55]. Conversely, in contexts where individuals are motivated to respond normatively, informant-reports can be more useful than self-report [56].

The relative utility of self- and informant-report data has been carefully studied in twin research, which find genetic convergence between informant- and self-report. Twin studies suggest that different informants appear to measure a largely common genetic liability, but there are also rater-specific genetic effects [57–59]. Accordingly, a GWAS of childhood aggressive behavior found that SNP-based heritability ranged from 4% for father-report to 8% for teacher-report [60]. Genetic correlations between informants ranged from $r_g = 0.46$ between self- and teacher-assessment to $r_g = 0.81$ between mother- and teacher-assessment (phenotypic correlations among raters ranged between 0.22 and 0.65), and genetic correlations with other forms of psychopathology were moderated by informant. These findings need to be replicated in other molecular genetic analyses, but show promise for aggregating data across multiple sources [61]. In sum, the optimal source, or sources, of information vary between forms of psychopathology and assessment contexts.

## BIOLOGICAL & BEHAVIORAL PHENOTYPES

Biological, especially neurological, and behavioral phenotypes show promise as targets for GWAS. Endophenotypes are intermediate phenotypes between genetic risk and psychopathology that are independent of illness state [62, 63]. Because endophenotypes are theoretically "closer to the gene", it has been hypothesized that their genetic underpinnings are less polygenic and less influenced by environment than psychiatric diagnoses, and therefore constitute a more powerful GWAS phenotype. These hypotheses continue being studied, but some endophenotypes' utility for gene discovery is supported by comparisons of the genetic architecture of psychiatric, neurological, and structural traits [64, 65]. GWAS of Alzheimer's disease and stroke endophenotypes, even of relatively small sample size ($N = 3146$ and 2471, respectively), have identified significant loci that converge with larger GWAS of those disorders [66–68]. Endophenotypes of schizophrenia, e.g. oculomotor inhibition and directed attention measured on the antisaccade task [69], and alcohol dependence, e.g. fast beta (20–28 Hz) electroencephalogram (EEG) oscillatory activity [70], show similar promise, as have biomarkers such as chronotype [71].

Biological and behavioral phenotypes need not be mediators between genetic risk and psychopathology to function as useful targets for GWAS. Some endophenotypes might simply be more feasible to collect than clinical data, or might serve as more objective and reliable markers of psychopathology than self-report, as discussed in sections above. Cotinine, a nicotine

metabolite, may be a more accurate endophenotype than self-reported tobacco use, if differences in body mass and metabolism confound self-reported severity measures such as packs-per-day. Indeed, cotinine GWAS have identified several significant associations [72, 73], despite relatively small sample sizes ($N = 5185$ and 4548). Relatively common behaviors and normal personality traits can also serve as GWAS endophenotypes, because individual differences in such behaviors can be markers of vulnerability to psychopathology [74–76]. For example, risk-taking behavior is not necessarily pathological, but it is useful both in predicting and understanding mental health problems such as alcohol use disorder or conduct disorder. Analyses of the risk-taking PGS in validation samples has revealed links between risk-taking and altered neuroanatomy, which may ultimately inform the understanding of externalizing disorders such as addiction [77]. Other endophenotypes relevant to psychiatric conditions that were successfully employed in GWAS include disinhibition and number of sexual partners [74], loneliness and social withdrawal [78, 79], subjective well-being [21], and employment in leadership roles [80].

Ultimately, the utility of biological and behavioral phenotypes for psychiatric GWAS will depend on the association between those phenotypes and psychopathology. However, early GWAS of phenotypes at multiple levels of analysis have resulted in novel genetic findings and constitute valuable additions to diagnostic GWAS. This suggests that endophenotypes will continue to constitute a powerful approach to identifying loci associated with complex psychiatric traits, and should be included in data collection for GWAS.

## COURSE OF ILLNESS PHENOTYPES

Longitudinal phenotypes allow the stable 'trait' element of psychopathology to be investigated separately from the 'state' element to increase power for genetic discovery. As first demonstrated in twin studies, phenotypes reflecting temporal stability or agreement over measures have a higher heritability than phenotypes measured at individual assessments [81, 82]. In molecular genetic research, Cheesman et al. [61]. observed an analogous phenomenon. SNP-based heritability estimates increased from an average of 5% (not significant) for individual state measures to 14% ($p = 0.002$) for an emotional problems trait constructed from 12 measures spanning 9 years. This is consistent with the view that genetics constitute core vulnerability to psychopathology that is best captured by stable, trait-like phenotypes. Time-specific phenotypes are more likely to be under transient environmental influences and have lower assessment reliability (i.e., more measurement error). Furthermore, cross-sectional assessments of rare, episodic phenotypes such as mania likely miss substantial variance. The frequency of mania appears to be a more robust indicator of genetic risk than cross-sectional measures of psychosis or mania [83].

Longitudinal phenotypes can also take the form of temporal illness features. Age of onset has been shown to be an indicator of genetic risk for depression [84], and when used as moderator, can increase GWAS power. Incorporating age of onset of ADHD revealed additional genome-wide significant associations, relative to a case-control design that did not account for age of onset [85]. Moreover, a recent GWAS found that SNP-based heritability was three times higher for early-onset MDD (onset at or before age 30) as compared to late-onset MDD (onset at or after age 44, $h_{SNP} = 0.130$ vs 0.043, respectively) [86]. Similarly, MDD with recurrent features may be more heritable than single episode MDD ($h_{SNP}$=0.107 vs 0.082, respectively). Finally, GWAS stratified by these temporal features identified additional six genome-wide significant loci (3 loci for early-onset MDD and 3 loci for recurrent MDD) [87]. While some GWAS, e.g., schizophrenia and anorexia nervosa age of onset GWAS, have not identified significant associations [88, 89], this may be attributable to small sample sizes.

Treatment resistance is another clinical feature that has resulted in new genetic discoveries. Treatment-resistant depression might be more heritable than non-treatment-resistant depression ($h_{SNP}$=0.23 vs 0.17, respectively) [87]. The correlation between the two depression phenotypes is significantly different from 1 ($r_g$=0.78), suggesting that although the two phenotypes are closely related, treatment resistance could provide novel genetic signal. Similarly, a GWAS of treatment resistant schizophrenia is useful not only as an additional phenotype with potential clinical utility [90], but also because it may be a more precise phenotype for identifying distinct etiological pathways. Variants increasing risk for treatment resistant schizophrenia may indicate a parallel pathway to psychosis that is non-overlapping with the dopaminergic pathway modulated by antipsychotics.

Longitudinal analyses can also inform our understanding of how genetic architecture changes over the lifespan. Cheesman et al. [61]. demonstrated that stable emotional problems in youth had only a moderate genetic correlation with adult depression and anxiety (average $r_g = 0.52$), implying distinct genetic liabilities at different ages. However, genetic risk for antisocial behavior based on GWAS performed in adults was associated with several antisocial outcomes across the lifespan [91]. Such comparisons could reveal how genetic risk changes or persists over development. However, there is a disconnect between GWAS in youth and adult samples. Studies of adults lack a life-course lense, and for many phenotypes GWAS in youth and adults are conducted by independent consortia—e.g. GWAS of antisocial behavior in adults [91] and GWAS of childhood aggressive behavior [60]. Connections between these findings remain to be explored. For many phenotypes (e.g. PTSD), GWAS in child and adolescent samples do not yet exist.

## PHENOTYPE/SAMPLE INTERACTIONS

For both quantitative and diagnostic phenotypes, it is important to consider how phenotype operationalization affects sample selection, and how any selection bias impacts subsequent GWAS. Case-control designs often use super-healthy controls, e.g. controls screened for the target *and* related phenotypes. Controls typically differ from cases on characteristics unrelated to the psychopathology of interest, such as intelligence, socio-economic status, and co-occurring mental health symptoms [92–94]. Such artifacts tend to be magnified when super-healthy controls are additionally screened for related psychopathology, or psychopathology among relatives. Use of such super-healthy control groups substantially inflates genetic correlations between traits [95]. Furthermore, individuals with severe symptoms experience more functional impairment, psychiatric, somatic, and physical comorbidities, and other burdens. These phenotypes are different from the trait of interest, but might be included in its measurement, e.g., impairment is often required to derive a clinical diagnosis in a case-control design, but may have distinct genetic risk factors, operating as an unmeasured confounder. Because there is no need to define groups for dimensional GWAS, samples may naturally be more heterogeneous, avoiding this source of confounding.

However, quantitative phenotypes are not immune from selection bias. Phenotypes collected through online portals require individuals have access to a smartphone or computer, and some degree of technological literacy. In UK Biobank, Mendelian randomization analyses indicate neuroticism and schizophrenia decreased the odds of participation in optional assessments, including a mental health questionnaire [96]. Consent to have one's 23andMe data used for research is non-random [97, 98], but it is difficult to study how this affects the resulting GWAS, as doing so would require performing research

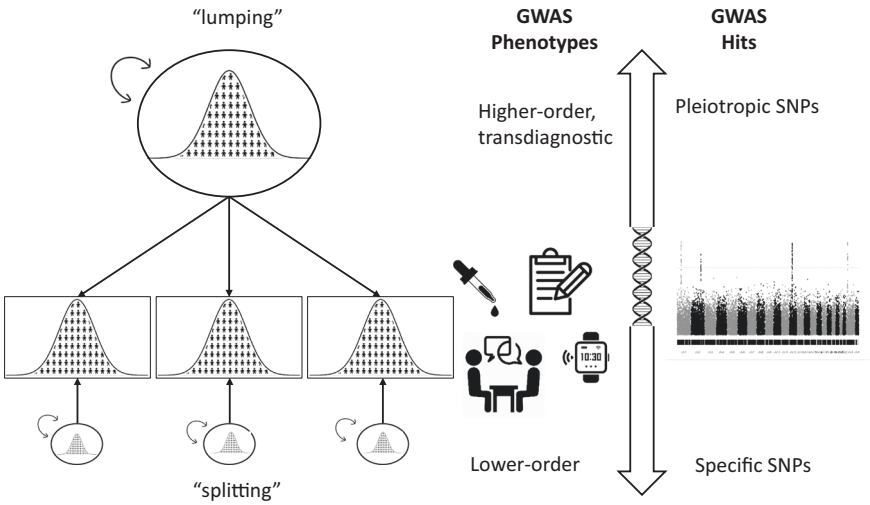


**Fig. 2 "Lumping" and "Splitting" of dimensional GWAS phenotypes.** Dimensional and transdiagnostic phenotypes can be measured using various sources of information, such as interview, self-reports, tissue samples, passive sensors, and other biological and behavioral markers. Variance (either phenotypic, or genetic if using genomic SEM) that is common to all measured phenotypes can be statistically "lumped" into a single higher-order phenotype, which can enhance GWAS power and result in discovery of pleiotropic SNPs. Simultaneously, variance that is unique to the measured phenotype can be statistically "split" into a lower-order phenotype, which can result in additional SNP discoveries with higher phenotype-specificity.

on individuals who have opted out of research. Illness course phenotypes are only identified among symptomatic individuals. The effect of such selection on power for gene discovery is unclear. Alternatively, it may be possible to collect behavioral phenotypes for individuals whose symptoms are too severe to allow for completion of a structured interview, reducing selection bias. In sum, failure to account for the factors affecting study participation can lead to spurious associations and incorrect biological inferences [99], regardless of phenotype.

## TRANSDIAGNOSTIC VERSUS SPECIFIC PHENOTYPES

"Lumping" and "splitting" phenotypes into broader, transdiagnostic phenotypes and narrower, specific, constructs, respectively, may increase power for gene discovery by capitalizing on patterns of genetic covariance (Fig. 2). Transdiagnostic phenotypic targets are consistent with a longstanding hypothesis that patterns of phenotypic covariance mimic patterns of genetic covariance [100]. This hypothesis has first been supported in the literature on plant and animal genomics and has been observed for most psychological traits observed in humans [101]. The "lumping" and "splitting" approaches result in hierarchical phenotypes that are based on longstanding empirical evidence that psychopathology's genetic architecture is also hierarchical, with some genes influencing broad (i.e., higher-order) psychiatric phenotypes and others a specific (i.e., lower-order) phenotype [102–106].

The "lumping" approach may be particularly useful when there is evidence that a general phenotype is more heritable than the specific phenotype. In the case of intelligence, the heritability of individual subtests, e.g. working memory, is largely explained by general intelligence [107]. Accordingly, a general intelligence GWAS in a modestly sized sample ($N = 35{,}298$) returned a relatively high SNP-based heritability of 0.22 [108]. An analysis of multiple cognitive phenotypes within the UK Biobank data is also informative [109]. Participants completed a tests of fluid intelligence, visual memory, and reaction time, all of which were approximately equal in length. The SNP-based heritability of fluid intelligence was 0.31, while the heritability of reaction time was 0.11 and visual memory was 0.05. The fluid intelligence phenotype was much more heritable than that for the specific cognitive abilities, despite the sample size for this phenotype being less than one-third that of specific phenotypes. It is difficult to disentangle the effects of test reliability, trait stability, and pleiotropy in these analyses, but each of these factors favors the use of higher-order phenotypes to improve statistical power for gene discovery.

Higher-order phenotypes may also be useful for moderately heritable but highly correlated phenotypes. Salient examples include anxiety disorders, which are highly genetically correlated in twin studies [110–112]. A genetic liability for anxiety may be shaped by specific environmental exposures (e.g., a dog bite, a trauma), resulting in any number of specific phobias in line with the general genes hypothesis [113]. Consistent with this hypothesis, the largest anxiety GWAS have combined all anxiety disorders to maximize sample size and power, akin to the fear factor [33, 114–117]. Notably, information is additive [118]. To the extent that any two measures of the same construct are correlated—that is, assess a common construct—a phenotype that combines data from both measures will be more powerful than either measure alone. The property underlies the utility of multi-trait methods such as genomic SEM [102] and multi-trait analysis of GWAS (MTAG) [119], when multiple phenotypes are available for the same individuals. Higher-order phenotypes may be especially useful in conditions with significant heterotypic continuity, such as eating disorders, in which high genetic risk may manifest as any number of different behaviors—binge eating, restricting, purging—over time [120–123]. More generally, due to shifts among different successive disorders [124], a higher-order general psychopathology factor (p-factor) may serve as a phenotype that captures genetic vulnerability to psychopathology across the lifespan. Higher-order phenotypes have more often been statistically inferred than measured directly using a dedicated instrument. That is, rather than assessing internalizing directly, genetic risk for internalizing is quantified through genetic covariance among more specific internalizing phenotypes, such as depression, anxiety, and PTSD, using genomic SEM [102, 103, 125] as well as other meta-analytic approaches such as MTAG [119]. Given the parallels between phenotypic and genetic patterns of covariance, these two approaches should converge. Box 1 discusses results from genomic SEM as an indication of how higher-order phenotypes may be useful targets for GWAS.

**Box 1.** Genomic SEM

Genomic structural equation modeling (SEM) studies identify patterns of genetic covariance among results from multiple GWAS. The findings to date suggest that many genes broadly influence liability to numerous psychiatric disorders [102, 103, 125]. In a prominent example, a GWAS of a broad, dimensional externalizing phenotype obtained using genomic SEM identified 579 genome-wide significant loci, 121 of which were not discovered in disorder-specific GWAS of any of the seven phenotypes comprising the broad externalizing [125]. Genetic risk for externalizing predicted many useful phenotypes in independent samples, including opioid use and suicide, phenotypes that have been difficult to predict even from GWAS specific to those phenotypes, although this enhanced discovery is driven at least in part by a much larger sample size of the genomic SEM-derived externalizing phenotype. Using a similar approach, a genomic SEM identified two transdiagnostic genetic factors, broadly corresponding to internalizing and thought disorder spectra, that in turn yielded novel and spectrum-specific loci in GWAS [150]. In an analysis that identified genetic risk at its broadest, the general factor of psychopathology, genomic SEM identified 128 loci with a sample size of 321,901 [102]. Notably, a cross-disorder meta-analysis, which is equivalent to a case-control design on the same phenotype, yields around the same number of SNPs (136) with a much larger sample size of 727,126 [6]. Taken together, phenotypes based on patterns of genetic covariance have the potential to increase the power of GWAS, as these phenotypes will parallel the structure of genetic influences. Consistent with these insights from genomic SEM, recent GWAS focus on phenotypes that represent major dimensions underlying numerous psychiatric conditions (e.g. the internalizing factor) [51], as well as on tight-knit lower-order phenotypes (e.g. anhedonia, suicidal ideation) [86, 131, 151].

If specific phenotypes are heterogeneous, "splitting" may be a preferred approach to capture additional lower-order influences. Indeed, GWAS of individual items from a dimensional depression measure (Patient Health Questionnaire-9; PHQ-9) [126] yielded 7 associations as compared to 4 obtained using the sum-score [127]. Results revealed genetic heterogeneity in depressive symptoms with no overlap in significant loci across PHQ-9 items. Genetic correlations between depressive symptoms ranged from moderate ($r_g < 0.60$) to very strong ($r_g > 0.90$). The underlying genetic structure between symptoms was best explained by two very strongly correlated genetic factors: psychological and somatic ($r_g = 0.93$). In a similar analysis, a set of GWAS of 16 clinically-informed MDD phenotypes (e.g. MDD with suicidal thoughts, postpartum depression) identified 47 independent genomic loci, a third of which were undetected in the latest MDD GWAS, despite that analysis having five times more cases [86]. Most notably, MDD with vegetative (i.e., atypical) features showed only a moderate genetic correlation with MDD without vegetative features ($r_g = 0.55$), indicating considerable unique genetic etiology of these two subtypes. Moreover, MDD with vegetative features showed a moderate positive genetic correlation with BMI ($r_g = 0.40$) while non-vegetative MDD had a negligible correlation with BMI ($r_g = -0.09$). In sum, "splitting" the depression phenotype suggests that while some symptoms have high genetic overlap, a considerable amount of genetic variation is unique rather than shared, and 'split' phenotypes can be useful for detecting these liabilities. The "splitting" approach to phenotyping has also been successfully implemented for gene discovery in OCD [128] and autism spectrum disorder [129, 130].

"Splitting" can also be useful in identifying genetic liability to specific components which are observed transdiagnostically, such as anhedonia [131]. This narrow phenotype had significant SNP-based heritability and positive genetic correlations with MDD, schizophrenia, and bipolar disorder—diagnoses in which anhedonia is often observed. Similarly, a GWAS of suicide death has demonstrated that suicide is heritable (.16 on the liability scale), and identified genetic variants shared between suicide death and schizophrenia, bipolar disorder, and autism [132]. Furthermore, a recent study conducted GWAS of data-driven PTSD subscales: re-experiencing, hyperarousal, and avoidance [31]. Although PTSD subscales demonstrated very strong genetic correlations ($r_g > 0.90$), supporting the importance of a general genetic vulnerability to PTSD, genomic SEM showed that hyperarousal had a unique genetic association with MDD, anxiety, and neuroticism, hinting at transdiagnostic pathways linking these diagnoses.

"Splitting" can also be a useful approach for identifying methodological artifacts in GWAS. In an alcohol use GWAS, items measuring alcohol consumption was closely related to socio-economic status, whereas a distinct subset measuring alcohol-related problems better captures variance shared with pathological consumption [46]. This finding explained paradoxical genetic correlations between alcohol use disorder and better physical health [38]. Future GWAS could take the "splitting" approach to study whether other related phenotypes such as impairment or stressful life events have separate genetic underpinnings from psychopathology.

In conclusion, lumping can increase statistical power in contexts where genetic risk increases psychopathology at the broadest level, or in cases of true pleiotropy. "Splitting", however, may increase power to detect additional genetic risk, including the instances when specific symptoms or traits are observed across multiple heterogeneous phenotypes. Simulations evaluating how lumping and splitting capture genetic risk across a variety of genetic architectures would be informative for the design of future phenotyping efforts.

## QUANTIFYING GENETIC RISK VERSUS GENE DISCOVERY

The choice of target phenotypes for GWAS is not a purely statistical decision, but one that depends on the GWAS's purpose. If the purpose of performing a GWAS is to develop a PGS of automobile speeding propensity, the best predictor may be a GWAS of automobile speeding propensity [74]. However, if the GWAS for the target phenotype is based on a small sample size, a related phenotype for which a larger sample size exists will likely produce a more powerful PGS. For example, a PGS from the recent externalizing GWAS [125] predicts opioid use disorder, a phenotype that was not part of the externalizing GWAS and has not been associated with opioid use disorder PGS, as discussed in Box 1. Because information is additive, and psychiatric traits tend to be both phenotypically and genetically correlated, the best way to improve prediction may be to use multiple PGS for related phenotypes. Likewise, PGS for anthropometric traits are currently more closely associated with eating disorders than the PGS based on GWAS for anorexia nervosa [133], and PGS of traits emerging in late adolescence or adulthood, such as substance abuse, can nonetheless predict important outcomes among children, or other populations in which the phenotype is not observed.

However, GWAS are not purely for the purposes of developing PGS, but also gene discovery and understanding etiology. For instance, a recent analysis of polygenic risk for PTSD and lifetime trauma exposure determined that, while genetic risk for PTSD is partially explained by genetic risk for trauma, PTSD also has some unique genetic risk that is correlated with neuroticism and irritability, indicating an alternative pathway to pathology that is not necessarily via trauma [32]. Relatedly, PTSD was significantly more genetically correlated with recurrent MDD than with MDD in individuals not reporting trauma, likely because individuals with recurrent MDD experience more traumatic events and, hence, might share genetic vulnerability to trauma exposure [134]. If the aim of a proposed GWAS is to inform genetic pathways and downstream biological mechanisms for a specific psychiatric phenotype, a corresponding dimension, perhaps refined using the "splitting" approach, will likely be the optimal phenotype.

## MEASURING DIMENSIONAL AND TRANSDIAGNOSTIC PHENOTYPES

While genomic SEM and other meta-analytic approaches such as MTAG [119] infer empirically-based transdiagnostic phenotypes,

they depend on re-analysis of existing data and can therefore be constrained. For example, negative symptoms drive psychosocial impairment in psychotic disorders [135], and a negative symptoms GWAS would be of utility for etiological and translational research. However, genomic SEM has not identified a negative symptom factor, and without directly phenotyping negative symptoms, it may not be possible to capture genetic variants contributing to this important outcome. For negative symptoms and other dimensional, transdiagnostic phenotypes, empirically-validated classification systems can provide useful targets for gene discovery at every level of specificity [136]. Below, we highlight two systems that may be particularly well-suited for informing the assessment of mental health phenotypes for molecular genetic research.

First, the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium proposed a data-driven phenotypic classification system for a wide range of psychiatric disorders [136–138]. The methods used to identify the structure of psychiatric phenotypes within the HiTOP model are equivalent to the structural equation modelling methods that are used to identify the structure of genetic risk in genomic SEM as well as in multivariate twin studies. The phenotypic hierarchy in the HiTOP model makes comorbidity an explicit and predictable feature by classifying related phenotypes together into higher-order factors: superspectra of emotional dysfunction [139], externalizing [140], and psychosis[49]; subfactors such as fear, distress, mania, sexual problems and eating pathology within emotional dysfunction [139]. Moreover, the phenotypes in the HiTOP model are dimensional, in order to capture the continuous variation of mental health problems across all levels of specificity (i.e., "lumping" and "splitting").

The National Institute of Mental Health developed the Research Domain Criteria (RDoC) model to guide research on the neurobiological bases of psychopathology. RDoC provides another toolbox of novel phenotypes [141–143]. RDoC phenotypes are organized around dimensional biobehavioral systems that cross diagnostic boundaries in a similar way to the higher-order genomic SEM phenotypes. Although RDoC is not hierarchical, each system contains narrow phenotypic constructs and subconstructs that "split" each system. The Negative Valence Systems, for example, consists acute threat, potential threat, sustained threat, loss, and frustrative nonreward. Each construct/subconstruct is transdiagnostic, e.g., acute threat characterizes a wide range of disorders such as OCD, panic, and PTSD. Although HiTOP and RDoC models come from different research traditions, they have many commonalities and points of convergence [144].

## CONCLUSION

In recent years, psychiatric genetics research has incorporated a wide range of phenotypic targets to enhance genetic discovery. Some of the most promising options are dimensional and transdiagnostic measures, assessing constructs at varying levels of analysis that are empirically derived from our understanding of symptom co-occurrence. Other effective phenotypic targets incorporate novel sources of information, such as collateral informants, longitudinal data, test performance, and biological measures.

A great deal remains unknown regarding how dimensional and transdiagnostic phenotypes compare to case-control designs. While simulations have been useful in understanding how case prevalence affects power of case-control designs, it is unknown how this manipulation affects quantitative phenotypes, which may also benefit from oversampling. More broadly, this review focuses on the impact of quantitative phenotypes for GWAS and gene discovery, rather than genetic prediction. A comparison of the phenotypic profile of quantitative and diagnostic PGS was beyond the scope of this review, despite its relevance to characterizing the utility of these phenotypes for gene discovery. We discussed prominent examples in which performing a GWAS of a broad phenotype in a population sample improved prediction of specific, rare phenotypes in validation samples. However, further research is needed on the conditions under which this phenomenon holds, and at what cost to precision. Similarly, longitudinal phenotypes are a nascent field of gene discovery. How to incorporate longitudinal data in a way that captures stability as well as change and heterotypic continuity is needed. Finally, this review has focused on discovering common genetic variants, rather than rare variants. We hypothesize that dimensional phenotypes will be especially informative in studying rare variants, because rare variants are more common in patients with severe psychopathology [145–147], so power to detect rare variants should be enhanced by the ability to discriminate between cases of varying severity. Similarly, "lumping" may be useful for the discovery of rare variants, many of which increase risk for multiple forms of psychopathology (i.e., 16p11.2 duplication (MAPK3)) [147, 148]. However, there is little research on this topic.

Ultimately, exploring novel target phenotypes for psychiatric GWAS has the potential to accelerate gene discovery, increase our understanding of the etiology of mental illness, and improve the power and precision of genetic prediction.

## DATA AVAILABILITY

No empirical data was generated in this literature review. GWAS summary statistics used in Table 1 can be downloaded from the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/results-and-downloads/), dbGaP (accession number phs001672.v10.p1.), and Edinburgh DataShare (https://datashare.ed.ac.uk/handle/10283/3203).

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## AUTHOR CONTRIBUTIONS

MAW and KGJ conceptualized the study, conducted the literature review, and wrote the first draft of the manuscript. KGJ conducted secondary data analysis. All co-authors critically revised the manuscript drafts and approved the final version.

## COMPETING INTERESTS

CM Bulik reports: Shire (grant recipient, Scientific Advisory Board member); Lundbeckfonden (grant recipient); Pearson (author, royalty recipient); Equip Health Inc. (Stakeholder Advisory Board). Other authors declare no conflict of interest.

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