Published in final edited form as:

Mol Psychiatry. 2019 December ; 24(12): 1770–1778. doi:10.1038/s41380-019-0457-6.

Genomics and Psychological Resilience: A Research Agenda

Karmel W. Choi, PhD[1,2,3,4], **Murray B. Stein, MD, MPH**[5,6], **Erin C. Dunn, ScD**[1,3,4,7], **Karestan C. Koenen, PhD**[1,2,3,4], **Jordan W. Smoller, MD, ScD**[1,2,3,4]

[1]Department of Psychiatry, Massachusetts General Hospital, Boston, MA

[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston MA

[4]Stanley Center for Psychiatric Research, Broad Institute, Boston, MA

[5]Department of Psychiatry, University of California San Diego, La Jolla, California

[6]VA San Diego Healthcare System, San Diego, California

[7]Henry & Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA

Abstract

Although exposure to adversity increases risk for poor mental health outcomes, many people exposed to adversity do not develop such outcomes. Psychological resilience, defined broadly as positive emotional and/or behavioral adaptation to adversity, may be influenced by genetic factors that have remained largely unexplored in the era of large-scale genome-wide studies. In this Perspective, we provide an integrative framework for studying human genome-wide variation underlying resilience. We first outline three complementary working definitions of psychological resilience—as a capacity, process, and outcome. For each definition, we review emerging empirical evidence, including findings from positive psychology, to illustrate how a resilience-based framework can guide novel and fruitful directions for the field of psychiatric genomics, distinct from ongoing study of psychiatric risk and related traits. Finally, we provide practical recommendations for future genomic research on resilience, highlighting a need to augment cross-sectional findings with prospective designs that include detailed measurement of adversities and outcomes. A research framework that explicitly addresses resilience could help us to probe biological mechanisms of stress adaptation, identify individuals who may benefit most from prevention and early intervention, and ascertain modifiable protective factors that mitigate negative outcomes even for those at high genetic risk.

Correspondence: Karmel Choi, Ph.D., 185 Cambridge Street, Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston MA 02114, kwchoi (at) mgh.harvard.edu.

Conflict of Interest Disclosures:

Dr Choi, Dr Dunn, and Dr Koenen have no conflicts of interest to disclose. Dr Stein has in the past 3 years been a consultant for Actelion, Aptinyx, Dart Neuroscience, Healthcare Management Technologies, Janssen, Neurocrine Biosciences, Oxeia Biopharmaceuticals, Pfizer, and Resilience Therapeutics. Dr Stein owns founders shares and stock options in Resilience Therapeutics and has stock options in Oxeia Biopharmaceticals. Dr Smoller is an unpaid member of the Bipolar/Depression Research Community Advisory Panel of 23andMe.

Keywords

Resilience; genetics; trauma; genome-wide association; mental health; polygenic; Mendelian randomization

Introduction

Although exposure to adversity increases risk for poor mental health outcomes (1,2), many people exposed to adversity do not develop such outcomes (3,4). Psychological resilience—whereby individuals maintain or regain positive mental health and/or functioning despite adversity (5–7)—has long been thought to be determined by multiple influences (8), ranging from environmental factors (e.g., community and social resources) to cognitive-behavioral patterns (e.g., problem-solving, reframing). More recently, researchers have also studied the role of heritable genetic variation in shaping resilience. Results from twin studies suggest that between 31 to 52% of observed variance in resilience phenotypes can be explained by such genetic variation (9–11). A limited set of candidate gene studies have sought to validate genetic contributors to resilience (12–14) but have been generally criticized for a poor record of replication (15). More recently, genomic methods such as genome-wide association studies (GWAS) (16–18) and polygenic scoring (19,20) have proliferated along with large publicly available data resources such as the UK Biobank (21) and are now poised to enable well-powered human genetic research on psychological resilience. However, few studies have capitalized on the availability of comprehensive genotyping and large-scale data science to study this phenomenon.

This Perspective aims to address this gap by proposing an integrative framework for extending genome-wide approaches to resilience. To accomplish this goal, we first outline three working definitions of psychological resilience, and review emerging evidence from genome-wide data for each of these definitions. Although psychological resilience is inextricably linked to the study of psychiatric risk and related traits, we discuss how a resilience-based framework can guide distinct and fruitful directions for the field of psychiatric genomics. We then summarize directions for future genomic research on resilience, highlighting a need to augment cross-sectional findings with prospective designs that include detailed measurement of adversities and outcomes. By broadening the current scope of psychiatric genomics research, we may gain additional molecular insights to guide ongoing basic and clinical research in understanding how humans adapt successfully to stress and adversity.

An integrative genomic framework for studying resilience

The first step to extending genome-wide approaches to psychological resilience requires consensus on how resilience should be defined. Theoretical definitions of resilience have been discussed in detail elsewhere (22–25), typically requiring exposure to adversity and evidence of positive adaptation despite adversity. However, one debate in the field has been whether resilience can be meaningfully studied as: (1) a trait-like *capacity* that precedes adversity; (2) a dynamic *process* that unfolds during and after adversity; or (3) an *outcome*

following adversity (7,24–26). We argue that genome-wide data could be used to examine resilience through each of these interrelated definitions (Figure 1).

As shown in this model, some individuals may possess pre-existing characteristics, or "resiliency factors," that increase their general *capacity* for resilience. For example, individuals with high levels of dispositional optimism or cognitive ability may be able to generally cope more flexibly and regulate difficult emotions, including in the face of adversity (27). The genetic basis of these predisposing capacities could be studied through GWAS. Second, resilience is now thought to represent a dynamic *process* that unfolds in the aftermath of adversity (6,7), involving an interplay between predisposing capacities, other protective factors (e.g., situational resources, such as social support), and risk factors (e.g., pre-existing vulnerabilities; situational characteristics of the adversity, such as its type, timing, duration, and severity). Studies incorporating both genomic and environmental data may shed light on this process by examining genetic influences in combination with non-genetic risk and protective factors across time. Third, resilience can be evidenced by the subsequent *outcome*, whether absence of disorder, presence of positive functioning, and/or recovery to baseline following adversity (5). Thus, similar to psychiatric disorders, these outcomes could be studied in a GWAS context, but with several meaningful distinctions, as summarized in the following sections. Together, these definitions of resilience may provide complementary (or distinct) insights on adaptation across the continuum of exposure to adversity, reflecting shared (or unique) genetic underpinnings (28).

In the next section, we review emerging evidence for each of these definitions and discuss how novel features of a resilience framework (Figure 2) may broaden existing efforts in psychiatric genomics. Importantly, psychiatric genomics has traditionally focused on specific disorders or vulnerability traits in cross-sectional designs, rather than strengths-based factors and protective processes influencing broad adaptive outcomes across time. Through the lens of this resilience framework, we thus map out promising territory for genomic research.

Genetic factors underlying *capacity* for resilience

Rather than focusing on vulnerability and disease, a resilience framework **directs attention to traits that index positive psychological strengths (Feature A)**. Such traits do not require adversity to be present, but could exert beneficial effects when adversity occurs. Though not explicitly studied in the context of resilience, numerous affective, personality, and cognitive phenotypes known to facilitate adaptive coping (29) and buffer against negative psychiatric outcomes following traumatic events (30) have been examined in GWAS. For example, an early GWAS identified one genome-wide significant locus associated with positive affect, or the tendency to experience positive emotions (31), within a high-trauma sample of 2,522 African American individuals. This locus was correlated with brain and blood expression of microRNAs previously implicated in reward behavior and with activation of reward-related brain regions (N=55). However, a subsequent small study (N=82) of European individuals unselected for trauma exposure (32) did not fully replicate this finding. One of the earliest large-scale GWAS of subjective wellbeing (N=298,420)—encompassing positive affect and life satisfaction—identified three separate loci associated

with subjective wellbeing (33). A larger meta-analytic GWAS (N=388,538) leveraging genome-wide information from correlated traits (34) identified 49 independent loci associated with subjective wellbeing and supported a role for genes expressed in central nervous system tissues and related to dopaminergic neurons, startle response, and exploration of new environments.

Cognitive abilities, including intelligence (IQ), have also been widely conceptualized as a protective factor across development (35) and associated with absence of psychopathology in at-risk populations (36). Based on prospective evidence that lower IQ predicts later risk for psychiatric disorders in trauma-exposed individuals (37), IQ has been posited to be a marker of cognitive reserve that could buffer individuals from psychopathology following adversity (38). IQ and cognitive ability, as well as highly correlated phenotypes such as educational attainment, have been the subject of several large-scale GWAS (39–42), including a recent meta-analytic GWAS in 269,867 individuals that identified 205 independent genome-wide significant loci for intelligence (41), and a meta-analytic GWAS of educational attainment in over 1.1 million individuals that identified 1,271 genome-wide significant loci, yielding polygenic scores explaining 7 to 10% of variation in cognitive performance (42). Consistent with a potential role in resilience, these cognitive phenotypes have also been found to be inversely correlated genetically with psychopathology (r=−.10 to −.27) (40,41), though the causal nature of these relationships are not well understood.

Personality traits such as conscientiousness and extraversion have also been known to account for substantial variance in positive functioning and psychological adjustment (11,43). A GWAS of these traits (N=123,132 to 260,861) identified a total of six genome-wide significant loci that were subsequently associated in external databases with gene expression in brain tissues (44). Genome-wide variation associated with conscientiousness and agreeableness has also been inversely correlated with psychiatric disorders such as depression (44). Elsewhere, polygenic scores for extraversion, constructed by combining GWAS-estimated effects of loci across the genome into a single score, have been associated with several dimensions of psychosocial wellbeing, though still explain less than 1% of variation in these dimensions (45).

Emerging work has begun to more directly study capacity for resilience, including trait resilience (46,47)—a dispositional ability to cope effectively and “bounce back” from stress—which has been shown to protect against psychiatric disorders in the context of adversity (48). Despite twin studies estimating heritability around 40% (9,11), only one GWAS of trait resilience to our knowledge has been conducted (49). This GWAS of trait resilience (defined as perceived coping ability) was performed in a sample of US Army soldiers (N=11,492) and identified one independent genome-wide significant locus (rs4260523) located upstream of a gene (*DCLK2*) previously implicated in neuron survival and preferentially expressed in brain areas including the frontal cortex and hippocampus. Studies could extend this work by investigating the genomic basis of trait resilience in larger, population-based samples, as well as other heritable traits associated with stress adaptability such as emotion regulation, cardiovascular flexibility, and social affiliation (50–52).

Rather than motivating further GWAS of individual traits, a resilience framework is expected to **prioritize inquiry spanning multiple traits (Feature B)**. Individual traits, like positive affect or intelligence, should not be taken to constitute resiliency per se, but rather represent components—or ingredients—of resiliency. Given a wide array of traits likely associated with a capacity for resilience, future efforts may benefit from integrating GWAS results to assess genetic variation shared by these traits and conduct functional follow-ups, providing clues to underlying adaptive molecular mechanisms. A multivariate genome-wide-association meta-analysis (53) recently identified 304 independent loci linked to a wellbeing "spectrum" encompassing positive affect/life satisfaction and neuroticism/depression traits (N=2,370,390), pointing to gene expression in the prefrontal cortex and hippocampus, particularly the subiculum, and enrichment for GABA-related interneurons in these areas. Finally, a resilience framework **focuses on identifying opportunities to prevent psychiatric morbidity (Feature C)**, rather than solely addressing established disease. While GWAS literature has already suggested that traits such as positive affect may be inversely related to psychiatric risk at a genetic level (33,41,44), it remains unclear whether such inverse associations reflect true protective effects that could be targeted through preventive efforts. Such questions can be interrogated using causal inference methods such as Mendelian randomization, which leverages the properties of genetic data—i.e., independent and random assignment of alleles prior to life events—to bypass typical limitations of observational studies such as confounding and reverse causation (54). We recently applied this method to validate causal protective influences of educational attainment for PTSD (55) and physical activity for depression (56). Other heritable and putatively malleable resiliency factors could be tested in a similar framework to probe protective mechanisms and prioritize prevention strategies.

Genetic and environmental factors that contribute to resilience *processes*

A resilience framework by definition **implies the presence of challenge or adversity (Feature D)**. A growing number of studies in psychiatric genomics have incorporated measures of adversity. These studies have examined, for example, whether polygenic risk scores for psychopathology interact with life adversities (e.g., trauma exposure, stressful life events) to influence conditions such as depression (57–59), typically detecting main effects of both polygenic risk and these adversities, while evidence for interaction effects has been mixed (59). Similarly, genome-wide gene-environment studies have revealed inconsistent, though likely underpowered, interaction effects between adversities and variants across the genome (60,61).

Beyond the need for larger samples and detailed measurements of adversity to strengthen such efforts, a resilience framework again **shifts attention from risk to protective processes (Feature A)**. Studies incorporating genomic and environmental data are well suited to examine resilience processes in which genetic influences combine with other protective and risk factors to influence adaptive outcomes following adversity. A handful of studies have reported protective interactions between candidate gene profiles and early adversity on depression (62,63), though candidate approaches have now been criticized (15). Polygenic approaches that incorporate genome-wide variation are more robust, though inquiry with respect to resilience remains limited (64). High polygenic loading for a

protective trait and/or low polygenic loading for a vulnerability trait may buffer against negative effects of adversity. One study (65) demonstrating this approach examined whether polygenic scores for subjective wellbeing constructed from the large GWAS described earlier (33) could buffer the negative effect of spousal loss on depressive symptoms in a longitudinal cohort of aging individuals in the US. This study found that while these individuals generally experienced a spike in depressive symptoms following the death of a spouse, those with higher wellbeing polygenic scores showed significantly smaller increases in depression compared to those with lower wellbeing scores.

A resilience framework also motivates efforts to identify modifiable factors that could offset genetic risk. Such efforts have been demonstrated in other fields, with studies reporting that protective lifestyle factors can decrease risk for negative outcomes such as cardiovascular disease even among individuals at high genetic vulnerability indexed by polygenic risk (66). In the realm of psychiatry, studies have begun to adopt this approach. In a prospective cohort of US Army soldiers (N=3,900), we found that unit cohesion—support and respect between peers and with group leaders—was associated with reduced risk for new-onset depression even for individuals with high polygenic risk for depression (67). Another study in a population-based cohort (N=4,166) found that personal coping abilities (indexed by self-reported trait resilience) attenuated associations between polygenic risk for depression and actual depression, even when adjusting for vulnerability factors like neuroticism (68). These studies highlight novel opportunities to validate modifiable factors (e.g., mindsets, behaviors, environments) with protective effects in the face of genetic risk. Study of such factors may guide the design of targeted interventions to promote resilience in vulnerable populations.

Finally, a resilience framework **prioritizes longitudinal inquiry with implications for early intervention and prevention (Features B and E)**. It has been long theorized that resilience as a dynamic *process* is best understood via prospective studies that assess the effects of risk and protective factors across time (7,24). Cross-sectional studies of resilience are limited by potential confounding from contemporaneous reports of both outcomes and modifying factors. With richer longitudinal data before and after adversity, we may be able to ascertain sensitive periods where genetically vulnerable individuals are most susceptible to the effects of protective factors following adversity exposure, to inform the optimal timing of interventions.

Genetic factors associated with resilient *outcomes*

To date, few genome-wide studies have examined resilient outcomes following adversity. Resilient outcomes could be operationalized in several ways (Table 1). One definition consistent with current GWAS designs is the absence of psychiatric disorder. However, a major criticism of this approach would be effective equivalence to a GWAS of the disorder (i.e., switching case-control status, such that variants positively associated with disorder are simply those negatively associated with absence of disorder). As mentioned, a resilience framework **implies exposure to adversity (Feature D)**. Earlier GWAS work (N=9,599) has suggested that genetic contributions to psychiatric disorders like depression differ in groups exposed and unexposed to adversity (69). Thus, a more appropriate way to study resilient

outcomes may be to restrict GWAS analyses only to those individuals exposed to risk or adversity. An existing corollary of this approach is GWAS of posttraumatic stress disorder, where trauma exposure has typically been incorporated as an inclusion criteria (70,71). We have further demonstrated this approach in a GWAS where absence of new-onset psychiatric disorders (*i.e.*, MDD, GAD, PTSD, and panic disorder) was operationalized as outcome-based resilience in US Army soldiers who experienced high levels of deployment-related trauma exposure (49). While the resulting high-exposure subset was small (N=581), a genome-wide significant locus was identified downstream of *SLC15A5*, whereas no genome-wide signal was detected using the full sample of deployed soldiers (N=1,939). Although this work relies on necessarily smaller samples, statistical power could be enhanced by leveraging larger consortia where individual studies have data on adversity (for further considerations, see Table 1). Examining absence of disorder in individuals exposed to especially high levels of adversity may allow us to identify genetic variants related to resilience, rather than those associated with disorder or adversity exposure that would have otherwise been detected in the full sample.

Resilient outcomes could also be operationalized as quantitative traits conditioned on adversity exposure. A twin study using this approach (10) examined stressful life events as predictors of current internalizing symptom scores. The residuals of this regression model—i.e., individual deviations from average symptom scores predicted by stressful life events—were taken to represent relative resilience, where negative residual values indicated fewer internalizing symptoms than predicted by adversity. This resilience phenotype was found to be heritable at over 50% after adjusting for measurement error and situational influences from the environment (10). Genetic variants associated with this relative resilience may be those that enable individuals to adapt more or less efficiently than predicted by the level of adversity they have experienced—though remain to be identified. However, residuals usually remain correlated with the outcome itself, which raises caution for interpreting genetic signals for relative resilience as fully independent from disorder (for further considerations, see Table 1).

In addition, a resilience framework ideally **includes multiple domains of psychological functioning (Feature C)**. According to the dual-factor model of mental health, absence of disorder and presence of psychological wellbeing represent somewhat unique dimensions of mental health at both phenotypic and genetic levels (72,73). Consistent with this model, a recent GWAS of two phenotypes—resilience defined as absence of psychiatric symptoms following trauma exposure, and resilience defined as a trait reflecting adaptive coping abilities—indicated sizeable but incomplete genetic correlations between these phenotypes (r_g=.66) (49). Thus, fully assessing resilience may involve integrating information across domains. Resilience should be expected to manifest across multiple domains, since positive functioning solely in one domain (e.g., absence of PTSD) may mask costs or disabilities in others (25,74). Approaches that statistically combine information from both negative (e.g., symptom) and positive (e.g., wellbeing) domains of mental health may augment our ability to detect genetic influences on broad-based resilience, as one recent twin study has suggested (75). Furthermore, it is known that individuals with ongoing psychopathology can exhibit functional resilience, building meaningful and productive lives (28). GWAS may thus

be applied to investigate adaptive functional outcomes following exposure to stress or trauma (76). These include traits of positive functioning in adversity-exposed populations, such as post-traumatic growth following exposure to a natural disaster, which have been explored in relation to candidate genes (77) but not with genome-wide approaches.

Finally, a resilience framework **motivates a longitudinal perspective (Feature E)**. Longitudinal trajectories have been posited as the gold standard for assessing resilient outcomes (4). Trajectories incorporate dynamic temporal information around adversity exposure to distinguish between stable absence of negative symptoms across time (i.e., "minimal impact" resilience) versus initial declines in mental health followed by recovery (i.e., "emergent" resilience) (78)—each linked to different factors and consequences (4) but easily conflated in cross-sectional assessments. Trajectories can be derived from longitudinal data with repeated measures of mental health following an adversity exposure, though such data are difficult to collect at large scale. For this, it may be possible to draw on naturalistic databases with longitudinal data, such as population registries or electronic health records. In addition, standard trajectory analyses involve probabilistically classifying individuals into one of several trajectory groups, leading to multinomial outcomes that remain challenging to model statistically in existing GWAS frameworks (for further considerations, see Table 1).

Conclusions and recommendations for future research

Large-scale, genome-wide studies of psychological resilience show great promise for expanding foundational information on mechanisms underlying adaptation to stress and trauma, which could be taken forward into molecular, translational, and clinical studies. To fulfill this promise, we recommend that future studies (a) **clearly define resilience**, **whether as a capacity, process, or outcome**. Different definitions may tap into complementary manifestations of psychological resilience and provide cumulative insights into human adaptation. Explicitly defining the phenotype(s) under study, as well as the domains and time frames in which these phenotypes are manifesting, will enable replication and interpretation. For example, absence of PTSD six months following acute trauma may be a different form of "resilience" than the broad presence of positive functioning despite a cumulative lifetime burden of traumatic events, though both may be of public health relevance. Second, we recommend that studies (b) **capitalize on more nuanced approaches for studying resilience** (Figure 2)—by explicitly accounting for adversity exposure, shifting attention to protective traits and processes, and emphasizing cross-domain and longitudinal inquiry for broad-based prevention. While resilience as an outcome or process could be approximated in cross-sectional studies with retrospective data, prospective studies with detailed measurement of adversities and outcomes provide the most rigorous design. Genomic studies are often limited in their longitudinal follow-ups and/or phenotyping. In the absence of ideal data, one practical way to study resilience at scale is to (c) **use insights from observational prospective literature to select targets for genomic discovery in large cross-sectional studies** (e.g., conducting a GWAS on trait optimism based on its known protective associations with mental health), **then validate discoveries in smaller but more richly phenotyped studies** (e.g., testing polygenic risk scores for optimism in relation to adaptive processes or outcomes). Over the long term, it will be critical to (d) **develop genomic consortia for longitudinal cohorts with well-characterized adversity exposures**

and outcomes, where genome-wide data can be pooled using harmonized resilience phenotypes, and possibly (e) **integrate dynamic signatures (e.g., epigenetic markers) of adaptive processes across time**, which were beyond the scope of this Perspective.

A focus on resilience aligns with efforts to identify protective genomic factors in health and disease (79,80) and emerging research in precision psychiatry to guide targeted and effective approaches to prevention and early intervention (81). Such efforts may help us better understand genetic sources of stress adaptation in the search for biological mechanisms. In turn, this work may allow us to distinguish individuals at relatively higher genetic propensity for adaptive traits and those who may benefit from further intervention, and to identify modifiable factors that could mitigate negative outcomes even for those at high genetic risk.

Acknowledgements and Funding

We would like to thank Kristen Nishimi, MPH, and Christy Denckla, PhD, for formative discussions and ongoing collaborations on resilience. Dr Choi was supported in part by a National Institute of Mental Health (NIMH) grant T32MH017119. Dr Smoller is a Tepper Family Massachusetts General Hospital Research Scholar and supported in part by the Demarest Lloyd, Jr. Foundation and NIMH grant K24MH094614. Dr Dunn was supported by a National Institute of Mental Health grant R01MH113930. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Breslau N Epidemiologic Studies of Trauma, Posttraumatic Stress Disorder, and other Psychiatric Disorders. The Canadian Journal of Psychiatry. 2002 12;47(10):923–9. [PubMed: 12553127]
2. Sayed S, Iacoviello BM, Charney DS. Risk Factors for the Development of Psychopathology Following Trauma. Current Psychiatry Reports [Internet]. 2015 8 [cited 2018 Jun 23];17(8). Available from: http://link.springer.com/10.1007/s11920-015-0612-y
3. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ. National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria: DSM-5 PTSD Prevalence. Journal of Traumatic Stress. 2013 10;26(5):537–47. [PubMed: 24151000]
4. Galatzer-Levy IR, Huang SH, Bonanno GA. Trajectories of resilience and dysfunction following potential trauma: A review and statistical evaluation. Clinical Psychology Review. 2018 7;63:41–55. [PubMed: 29902711]
5. Rutter M Implications of Resilience Concepts for Scientific Understanding. Annals of the New York Academy of Sciences. 2006 12 1;1094(1):1–12.
6. Luthar SS, Cicchetti D, Becker B. The construct of resilience: a critical evaluation and guidelines for future work. Child Dev. 2000 6;71(3):543–62. [PubMed: 10953923]
7. Kalisch R, Baker DG, Basten U, Boks MP, Bonanno GA, Brummelman E, et al. The resilience framework as a strategy to combat stress-related disorders. Nature Human Behaviour. 2017 11;1(11):784–90.
8. Cicchetti D Resilience under conditions of extreme stress: a multilevel perspective. World Psychiatry. 2010 10;9(3):145–54. [PubMed: 20975856]
9. Boardman JD, Blalock CL, Button TMM. Sex Differences in the Heritability of Resilience. Twin Research and Human Genetics. 2008 2;11(01):12–27. [PubMed: 18251671]
10. Amstadter AB, Myers JM, Kendler KS. Psychiatric resilience: longitudinal twin study. British Journal of Psychiatry. 2014 10;205(04):275–80. [PubMed: 24723629]
11. Waaktaar T, Torgersen S. Genetic and Environmental Causes of Variation in Trait Resilience in Young People. Behavior Genetics. 2012 5;42(3):366–77. [PubMed: 22101958]
12. Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. Nat Rev Neurosci. 2009 6;10(6):446–57. [PubMed: 19455174]

13. Kim-Cohen J, Turkewitz R. Resilience and measured gene–environment interactions. Development and Psychopathology. 2012 11;24(04):1297–306. [PubMed: 23062298]
14. Bowes L, Jaffee SR. Biology, Genes, and Resilience: Toward a Multidisciplinary Approach. Trauma, Violence, & Abuse. 2013 7;14(3):195–208.
15. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry. 2011 10;168(10):1041–9. [PubMed: 21890791]
16. Wray NR, eQTLGen, 23andMe, the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nature Genetics. 2018 5;50(5):668–81. [PubMed: 29700475]
17. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nature Communications [Internet]. 2017 12 [cited 2018 Aug 17];8(1). Available from: http://www.nature.com/articles/s41467-017-01261-5
18. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet. 2018 7;50(7):920–7. [PubMed: 29942085]
19. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics [Internet]. 2018 8 13 [cited 2018 Aug 17]; Available from: http://www.nature.com/articles/s41588-018-0183-z
20. Wray NR, Lee SH, Mehta D, Vinkhuyzen AAE, Dudbridge F, Middeldorp CM. Research review: Polygenic methods and their application to psychiatric traits. J Child Psychol Psychiatry. 2014 10;55(10):1068–87. [PubMed: 25132410]
21. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLOS Medicine. 2015 3 31;12(3):e1001779. [PubMed: 25826379]
22. Bonanno GA. Uses and abuses of the resilience construct: Loss, trauma, and health-related adversities. Social Science & Medicine. 2012 3;74(5):753–6. [PubMed: 22300714]
23. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. Behavioral and Brain Sciences. 2014 8 27;1–49. [PubMed: 24461214]
24. Luthar SS, Cicchetti D, Becker B. The construct of resilience: a critical evaluation and guidelines for future work. Child Dev. 2000;71(3):543–62. [PubMed: 10953923]
25. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. European Journal of Psychotraumatology. 2014 12;5(1):25338.
26. Niitsu K, Houfek JF, Barron CR, Stoltenberg SF, Kupzyk KA, Rice MJ. A Concept Analysis of Resilience Integrating Genetics. Issues in Mental Health Nursing. 2017 11 2;38(11):896–906. [PubMed: 28766971]
27. Nes LS, Segerstrom SC. Dispositional Optimism and Coping: A Meta-Analytic Review. Personality and Social Psychology Review. 2006 8;10(3):235–51. [PubMed: 16859439]
28. Yehuda R, Flory JD. Differentiating biological correlates of risk, PTSD, and resilience following trauma exposure. Journal of Traumatic Stress. 2007 8;20(4):435–47. [PubMed: 17721957]
29. Tugade MM, Fredrickson BL, Feldman Barrett L. Psychological Resilience and Positive Emotional Granularity: Examining the Benefits of Positive Emotions on Coping and Health. Journal of Personality. 2004 12;72(6):1161–90. [PubMed: 15509280]
30. Fredrickson BL, Tugade MM, Waugh CE, Larkin GR. What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. J Pers Soc Psychol. 2003 2;84(2):365–76. [PubMed: 12585810]
31. Wingo AP, Almli LM, Stevens JS, Jovanovic T, Wingo TS, Tharp G, et al. Genome-wide association study of positive emotion identifies a genetic variant and a role for microRNAs. Molecular Psychiatry. 2017 5;22(5):774–83. [PubMed: 27595594]

32. Lancaster TM, Ihssen N, Brindley LM, Linden DEJ. Further support for association between GWAS variant for positive emotion and reward systems. Translational Psychiatry. 2017 1;7(1):e1018–e1018. [PubMed: 28140400]
33. Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet. 2016;48(6):624–33. [PubMed: 27089181]
34. 23andMe Research Team Social Science Genetic Association Consortium, Turley P, Walters RK, Maghzian O, Okbay A, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. Nature Genetics. 2018 2;50(2):229–37. [PubMed: 29292387]
35. Masten AS, Coatsworth JD. The development of competence in favorable and unfavorable environments. Lessons from research on successful children. Am Psychol. 1998 2;53(2):205–20. [PubMed: 9491748]
36. Tiet QQ, Bird HR, Davies M, Hoven C, Cohen P, Jensen PS, et al. Adverse Life Events and Resilience. Journal of the American Academy of Child & Adolescent Psychiatry. 1998 11;37(11): 1191–200. [PubMed: 9808931]
37. Breslau N, Chen Q, Luo Z. The Role of Intelligence in Posttraumatic Stress Disorder: Does it Vary by Trauma Severity? Seedat S, editor. PLoS ONE. 2013 6 10;8(6):e65391. [PubMed: 23762357]
38. Koenen KC, Moffitt TE, Roberts AL, Martin LT, Kubzansky L, Harrington H, et al. Childhood IQ and Adult Mental Disorders: A Test of the Cognitive Reserve Hypothesis. American Journal of Psychiatry. 2009 1;166(1):50–7. [PubMed: 19047325]
39. Davies G, Armstrong N, Bis JC, Bressler J, Chouraki V, Giddaluru S, et al. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). Molecular Psychiatry. 2015 2;20(2):183–92. [PubMed: 25644384]
40. Trampush JW, Yang MLZ, Yu J, Knowles E, Davies G, Liewald DC, et al. GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. Molecular Psychiatry. 2017 3;22(3):336–45. [PubMed: 28093568]
41. Sniekers S, Stringer S, Watanabe K, Jansen PR, Coleman JRI, Krapohl E, et al. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. Nature Genetics. 2017 5 22;49(7):1107–12. [PubMed: 28530673]
42. 23andMe Research Team, COGENT (Cognitive Genomics Consortium), Social Science Genetic Association Consortium, Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nature Genetics. 2018 8;50(8):1112–21. [PubMed: 30038396]
43. Campbell-Sills L, Cohan SL, Stein MB. Relationship of resilience to personality, coping, and psychiatric symptoms in young adults. Behaviour Research and Therapy. 2006 4;44(4):585–99. [PubMed: 15998508]
44. Lo M-T, Hinds DA, Tung JY, Franz C, Fan C-C, Wang Y, et al. Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. Nat Genet. 2017;49(1):152–6. [PubMed: 27918536]
45. Weiss A, Baselmans BML, Hofer E, Yang J, Okbay A, Lind PA, et al. Personality Polygenes, Positive Affect, and Life Satisfaction. Twin Res Hum Genet. 2016;19(5):407–17. [PubMed: 27546527]
46. Connor KM, Davidson JRT. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). Depression and Anxiety. 2003 9;18(2):76–82. [PubMed: 12964174]
47. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): Validation of a 10-item measure of resilience. Journal of Traumatic Stress. 2007 12;20(6):1019–28. [PubMed: 18157881]
48. Sheerin CM, Lind MJ, Brown EA, Gardner CO, Kendler KS, Amstadter AB. The impact of resilience and subsequent stressful life events on MDD and GAD. Depression and Anxiety. 2018 2;35(2):140–7. [PubMed: 29172241]
49. Stein MB, Choi KW, Jain S, Campbell-Sills L, Chen C, Gelernter J, et al. Genome-wide analyses of psychological resilience in U.S. Army soldiers. American Journal of Medical Genetics Part B:

Neuropsychiatric Genetics [Internet]. 2019 5 13 [cited 2019 May 14]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.b.32730

50. Hawn SE, Overstreet C, Stewart KE, Amstadter AB. Recent advances in the genetics of emotion regulation: a review. Current Opinion in Psychology. 2015 6;3:108–16. [PubMed: 27588302]
51. Navrady LB, Zeng Y, Clarke T-K, Adams MJ, Howard DM, Deary IJ, et al. Genetic and environmental contributions to psychological resilience and coping. Wellcome Open Research. 2018 2 15;3:12. [PubMed: 30345373]
52. Day FR, Ong KK, Perry JRB. Elucidating the genetic basis of social interaction and isolation. Nature Communications [Internet]. 2018 12 [cited 2018 Sep 5];9(1). Available from: http://www.nature.com/articles/s41467-018-04930-1
53. Baselmans BML, Jansen R, Ip HF, van Dongen J, Abdellaoui A, van de Weijer MP, et al. Multivariate genome-wide analyses of the well-being spectrum. Nat Genet. 2019 3;51(3):445–51. [PubMed: 30643256]
54. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?*. International Journal of Epidemiology. 2003 2;32(1):1–22. [PubMed: 12689998]
55. Polimanti R, Ratanatharathorn A, Maihofer AX, Choi KW, Stein MB, Morey RA, et al. Economic status mediates the relationship between educational attainment and posttraumatic stress disorder: a multivariable Mendelian randomization study: Supplemental Material. bioRxiv [Internet]. 2018 12 21 [cited 2019 Apr 3]; Available from: http://biorxiv.org/lookup/doi/10.1101/503300
56. Choi KW, Chen C-Y, Stein MB, Klimentidis YC, Wang M-J, Koenen KC, et al. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry [Internet]. 2019 1 23 [cited 2019 Mar 8]; Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2018.4175
57. Colodro-Conde L, Couvy-Duchesne B, Zhu G, Coventry WL, Byrne EM, Gordon S, et al. A direct test of the diathesis-stress model for depression. Mol Psychiatry. 2017 7 11;
58. Coleman JRI, Purves KL, Davis KAS, Rayner C, Choi SW, Hübel C, et al. Genome-wide gene-environment analyses of depression and reported lifetime traumatic experiences in UK Biobank. 2018 3 16 [cited 2018 Sep 5]; Available from: http://biorxiv.org/lookup/doi/10.1101/247353
59. Peyrot WJ, Van der Auwera S, Milaneschi Y, Dolan CV, Madden PAF, Sullivan PF, et al. Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5765 Subjects From the Psychiatric Genomics Consortium. Biol Psychiatry. 2017 9 21;
60. Van der Auwera S, Peyrot WJ, Milaneschi Y, Hertel J, Baune B, Breen G, et al. Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes: The childhood trauma working-group of PGC-MDD. Am J Med Genet B Neuropsychiatr Genet. 2018 1;177(1):40–9. [PubMed: 29159863]
61. Dunn EC, Wiste A, Radmanesh F, Almli LM, Gogarten SM, Sofer T, et al. GENOME-WIDE ASSOCIATION STUDY (GWAS) AND GENOME-WIDE BY ENVIRONMENT INTERACTION STUDY (GWEIS) OF DEPRESSIVE SYMPTOMS IN AFRICAN AMERICAN AND HISPANIC/LATINA WOMEN. Depress Anxiety. 2016 4;33(4):265–80. [PubMed: 27038408]
62. Bousman CA, Gunn JM, Potiriadis M, Everall IP. Polygenic phenotypic plasticity moderates the effects of severe childhood abuse on depressive symptom severity in adulthood: A 5-year prospective cohort study. The World Journal of Biological Psychiatry. 2017 1 2;18(1):75–81. [PubMed: 26878222]
63. Vrshek-Schallhorn S, Stroud CB, Mineka S, Zinbarg RE, Adam EK, Redei EE, et al. Additive genetic risk from five serotonin system polymorphisms interacts with interpersonal stress to predict depression. J Abnorm Psychol. 2015 11;124(4):776–90. [PubMed: 26595467]
64. Krapohl E, Euesden J, Zabaneh D, Pingault J-B, Rimfeld K, von Stumm S, et al. Phenome-wide analysis of genome-wide polygenic scores. Molecular Psychiatry. 2016 9;21(9):1188–93. [PubMed: 26303664]

65. Domingue BW, Liu H, Okbay A, Belsky DW. Genetic Heterogeneity in Depressive Symptoms Following the Death of a Spouse: Polygenic Score Analysis of the U.S. Health and Retirement Study. American Journal of Psychiatry. 2017 10;174(10):963–70. [PubMed: 28335623]
66. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. N Engl J Med. 2016 15;375(24):2349–58. [PubMed: 27959714]
67. Choi KW, Chen C-Y, Ursano RJ, Sun X, Jain S, Kessler RC, et al. Prospective study of polygenic risk, protective factors, and incident depression following combat deployment in US Army soldiers. Psychological Medicine. 2019 4 15;1–9.
68. Navrady LB, Adams MJ, Chan SWY, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Ritchie SJ, McIntosh AM. Genetic risk of major depressive disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression. Psychological Medicine. 2017 11 29;1–10.
69. Peterson RE, Cai N, Dahl AW, Bigdeli TB, Edwards AC, Webb BT, et al. Molecular Genetic Analysis Subdivided by Adversity Exposure Suggests Etiologic Heterogeneity in Major Depression. Am J Psychiatry. 2018 6 1;175(6):545–54. [PubMed: 29495898]
70. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, et al. Largest genome-wide association study for PTSD identifies genetic risk loci in European and African ancestries and implicates novel biological pathways. bioRxiv [Internet]. 2018 11 1 [cited 2019 Apr 5]; Available from: http://biorxiv.org/lookup/doi/10.1101/458562
71. Stein MB, Chen C-Y, Ursano RJ, Cai T, Gelernter J, Heeringa SG, et al. Genome-wide Association Studies of Posttraumatic Stress Disorder in 2 Cohorts of US Army Soldiers. JAMA Psychiatry. 2016 7 1;73(7):695–704. [PubMed: 27167565]
72. Kendler KS, Myers JM, Maes HH, Keyes CLM. The Relationship Between the Genetic and Environmental Influences on Common Internalizing Psychiatric Disorders and Mental Well-Being. Behavior Genetics. 2011 9;41(5):641–50. [PubMed: 21451959]
73. Routledge KM, Burton KLO, Williams LM, Harris A, Schofield PR, Clark CR, et al. Shared versus distinct genetic contributions of mental wellbeing with depression and anxiety symptoms in healthy twins. Psychiatry Research. 2016 10;244:65–70. [PubMed: 27472172]
74. Brody GH, Yu T, Chen E, Miller GE, Kogan SM, Beach SRH. Is resilience only skin deep?: rural African Americans' socioeconomic status-related risk and competence in preadolescence and psychological adjustment and allostatic load at age 19. Psychol Sci. 2013 7 1;24(7):1285–93. [PubMed: 23722980]
75. Wolf EJ, Miller MW, Sullivan DR, Amstadter AB, Mitchell KS, Goldberg J, et al. A classical twin study of PTSD symptoms and resilience: Evidence for a single spectrum of vulnerability to traumatic stress. Depression and Anxiety. 2018 2;35(2):132–9. [PubMed: 29283198]
76. McGrath LM, Cornelis MC, Lee PH, Robinson EB, Duncan LE, Barnett JH, et al. Genetic predictors of risk and resilience in psychiatric disorders: A cross-disorder genome-wide association study of functional impairment in major depressive disorder, bipolar disorder, and schizophrenia. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2013 12;162(8):779–88.
77. Dunn EC, Solovieff N, Lowe SR, Gallagher PJ, Chaponis J, Rosand J, et al. Interaction between genetic variants and exposure to Hurricane Katrina on post-traumatic stress and post-traumatic growth: a prospective analysis of low income adults. J Affect Disord. 2014 1;152–154:243–9.
78. Bonanno GA, Diminich ED. Annual Research Review: Positive adjustment to adversity - trajectories of minimal-impact resilience and emergent resilience: Annual Research Review - Positive adjustment to adversity. Journal of Child Psychology and Psychiatry. 2013 4;54(4):378–401. [PubMed: 23215790]
79. Harper AR, Nayee S, Topol EJ. Protective alleles and modifier variants in human health and disease. Nature Reviews Genetics. 2015 12;16(12):689–701.
80. Schwartz MLB, Williams MS, Murray MF. Adding Protective Genetic Variants to Clinical Reporting of Genomic Screening Results: Restoring Balance. JAMA. 2017 4 18;317(15):1527. [PubMed: 28288260]

81. Stein MB, Smoller JW. Precision Psychiatry—Will Genomic Medicine Lead the Way? JAMA Psychiatry. 2018 7 1;75(7):663. [PubMed: 29800947]

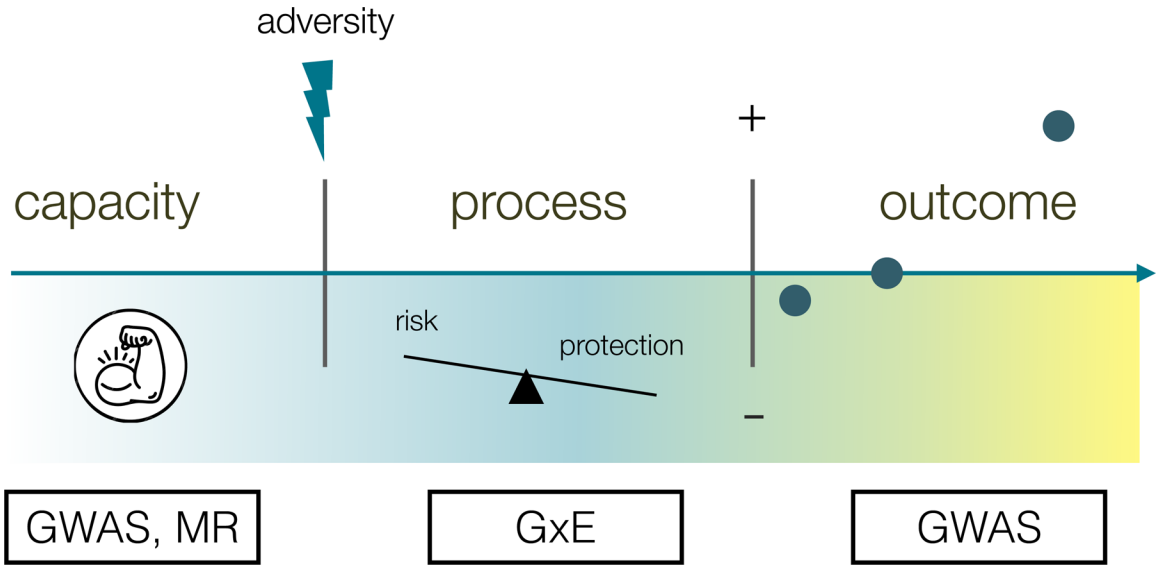

Figure 1.
Proposed integrative genomic framework for resilience. GWAS = genome-wide association studies. MR = Mendelian randomization studies. GxE = gene-by-environment studies.

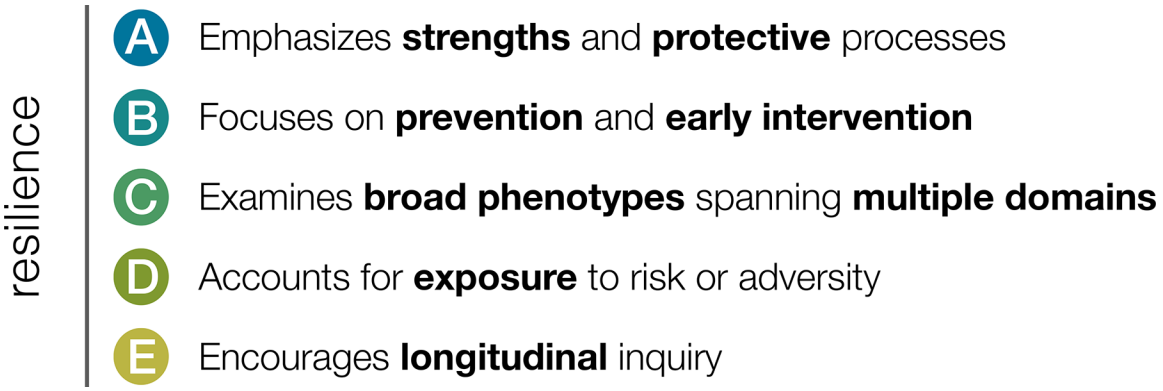

Figure 2.
Novel features of a resilience framework for psychiatric genomics.

Table 1.

Operationalizing resilience outcomes for GWAS

Resilience outcome	Advantages	Disadvantages
Absence of psychiatric disorder	Large sample sizes, similar to existing GWAS datasets	Inverse of GWAS for disorder, and thus limited new insights
Absence of psychiatric disorder in high adversity-exposed individuals	Available in existing datasets; may reveal unique signals distinct from full sample GWAS	Reduced sample size and statistical power for GWAS
Residual-based (i.e., of psychiatric symptoms and/or functioning regressed on adversity exposure)	Preserves larger sample size for GWAS; more fine-grained phenotype of relative resilience conditioned on adversity	Empirical derivation of resilience scores; requires adequate measurement of adversity; regression assumptions about influence of adversity exposure
Positive functioning (e.g., post-traumatic growth)	Focuses on potentially overlooked positive domains of resilience following adversity	Not yet widely collected in genomic studies
Resilient trajectories	Captures dynamic nature of resilience by studying recovery after exposure to adversity.	Requires longitudinal data; trajectory assignment resulting in multinomial outcomes, limiting sample size and power.