

## Strength in Numbers

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The National Institute of Mental Health (NIMH) maintains a comprehensive portfolio of research on depression risk, etiology, pathophysiology, intervention, and services research. This broad portfolio exists because, as with many of our illnesses, there is still much work to be done to identify potent intervention targets for treatment and prevention, develop novel interventions, optimize the effectiveness of the interventions we know to be efficacious, and develop the science to implement and sustain programs that work. With the goal of expediting scientific advances, NIMH encourages investigators in a given field to communicate, collaborate, and share knowledge, data, and resources. The papers presented in this special issue highlight a concerted, grassroots collaborative effort among the investigators in the field of depression prevention that resulted in a proactive, thoughtful sharing of ideas and sharing of individual-level data across studies. For the field, this collaboration presents an opportunity to “see the forest through the trees” and develop an understanding of the state of the science for depression prevention that goes beyond what we can learn from the report of an individual study.

The papers included in this special issue were authored by prevention scientists who are developing and testing interventions—some specifically targeting depression, others targeting

associated high-risk behaviors. Reading the papers as a set enables one to identify common findings and themes and allows us to see if an individual study’s effects change when participant-level data is combined and re-examined across a range of studies. This collaboration offers innovations not just in the data analysis and methodology, as described in the papers by Siddique et al. (2017) and Brincks et al. (2016), but also in our understanding of how we might enhance or alter existing interventions so we may more effectively prevent the incidence or recurrence of depression among vulnerable youth. The papers go beyond reporting only if an intervention works, but also for whom. A focus on moderators as well as possible mechanisms of action will further our ability to refine intervention strategies and, ultimately, prevent incidence of illness.

In the interest of space, we will not review all of the individual study findings but will, instead, highlight a few key outcomes across the papers. In doing so, we see that early intervention matters. Stronger effects tend to be found for groups who received interventions in earlier grades or earlier in the course of illness (i.e., before symptoms emerged). The set of papers also shows the ways in which family can be a key component to effective depression prevention. Across studies, aspects of the family moderate intervention effects—e.g., parent illness, parent marital status, and overall family functioning. In one study, family characteristics were more important than dose with respect to impact on internalizing behaviors (Mauricio et al. 2016).

This special issue also includes an article by Brown and colleagues which combines and re-analyzes participant-level data from 19 studies to identify moderators of intervention response. The rationale for the integrated approach is clear—oftentimes, individual studies are not sufficiently powered to examine effects of specific moderators of interest, and individual studies may take different approaches to conducting a moderator analysis, making the comparison of findings across studies challenging. The data included in the analyses by

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Brown et al. 2016 represent 19 trials of preventive interventions (including those with individual papers in this special issue) and 5210 adolescents. Results of the integrative data analysis suggest that individuals with higher levels of depressive symptoms at baseline respond more quickly to the interventions. Individual demographics (e.g., age, race/ethnicity) were not associated with changes in symptoms and the impact on depressive symptoms was greatest for those enrolled in depression-focused trials. It is possible that stronger effects were seen in the depression-focused trials because they were closer in form to treatment studies—enrolling symptomatic individuals who received what could be conceived of as modified treatment programs, delivered at a time when the individuals may not have met diagnostic criteria for illness. In contrast, while there were changes in depressive symptoms for individuals enrolled in behavioral or general mental health trials, the trajectory of change for individuals in those trials did not differ between intervention and control conditions. This may be due to more heterogeneity among the samples with respect to depressive symptoms.

Looking beyond depression, these studies illustrate the scientific benefit of cultivating a culture of information and data sharing. On the most basic level of information sharing, it is critical that investigators disseminate positive, negative, and unexpected findings. Unexpected results—such as the Brincks et al. (2016) “bonus” finding that an intervention designed for substance use prevention also impacts internalizing disorders—are important because they inform our understanding of “crossover” effects, expand the reach of interventions, and ultimately maximize efficiencies in prevention research (e.g., limiting the need for multiple trials of the same intervention to evaluate distinct but related outcomes). Indeed, in preparation for a recent NIH Office of Disease Prevention workshop focused on the impact of early intervention on downstream suicidal behavior, four teams of investigators who had developed and tested family-focused preventive interventions (including two reported in this issue—Family Check-up and Familias Unidas) examined their data and identified crossover effects; i.e., interventions not directly targeting suicide-related behavior actually reduced the onset of suicide ideation and attempts (Reider and Sims 2016). A summary of the workshop is publicly available, as are workshop recommendations, which include ways to overcome barriers that limit data sharing and data linkage in prevention research (Little et al. 2016). To that end, a recently published funding opportunity announcement (RFA-MH-18-400) issued by several NIH institutes encourages the integration of existing data sets for secondary analyses that might identify potential biological, experiential, or other predictors and moderators of suicide risk.

The crossover effects or bonus findings also serve to illustrate that heterogeneity is common—both in terms of response to intervention but also in terms of vulnerability to depression—and this needs to be accounted for. A one-size-fits-all approach is unlikely to have a substantial impact on rates of

depression. Attention to subgroups and differing patterns of response could enhance efficiency and result in more tailored approaches to prevention at the individual, family, or community levels. The field may also consider moving away from the notion of prevention as early treatment and focus on identifying modifiable risk factors that precede illness onset to target for future intervention development. There may be more to be gained by targeting mechanisms common across disorders as opposed to focusing on individuals displaying symptoms of a specific disease.

That interventions not specifically designed to impact depression or internalize behaviors had impacts on these outcomes affirms the notion that while we may, a priori, define a risk group based on factors such as genes, adverse childhood experiences, or symptoms/observed behaviors, there is often a lack of specificity in our ability to predict specific illness trajectories. Thus, while an investigator may design an intervention to target a specific outcome of interest, the common constructs that underlie our disorders suggest that one at-risk child could be on any number of trajectories with respect to diagnostic outcome. The impact of preventive intervention research may increase if we focus more on these common constructs and their underlying mechanisms, as suggested by the NIMH Research Domain Criteria (RDoC) initiative, and less on a specific disease category. A recent commentary offers perspectives on integrating RDoC into the development and testing of preventive interventions (see Goldstein and Morris 2016).

Future research should continue to focus on the role of the family in depression prevention, and include family variables as possible intervention targets. Family functioning, parental beliefs, and parent illness are all modifiable risk factors that can be targeted with existing efficacious approaches. The focus of the next phase of research, then, may be determining how to best stratify level of risk for depression as a function of these family-level variables, as that may inform who would benefit most from receipt of intervention. In times of increasingly limited resources, enhanced efficiency with respect to resource allocation is of utmost importance.

For those approaches that are efficacious, steps should be taken to expedite their implementation. In 2009, NIMH launched the Recovery After an Initial Schizophrenia Episode (RAISE) Project. Unique about this endeavor was the focus on deployment-focused intervention development—taking interventions that were known to be efficacious for a population, packaging them, and testing that package within “real-world” settings and using real-world payment systems to fund the care. Active partnerships between NIMH and other federal agencies throughout the life of the project allowed for rapid dissemination of the interventions at the national level after the study was completed and the packaged intervention demonstrated to be efficacious. This type of approach that capitalizes on partnerships and the rapid implementation of evidence should be considered for other areas,

such as depression prevention, where data on effective approaches to intervention continue to accumulate. NIMH supports science to study innovative approaches to implementation and service delivery via funding opportunity announcements (e.g., PAR-17-264, “Innovative Mental Health Services Research Not Involving Clinical Trials”); there are many questions to be asked with respect to implementation of preventive services.

In addition to the positive impacts of interventions, equally important are findings such as the ones presented by Brunswasser and Gillham (2016) where, looking across studies of the same intervention, the investigators found variable effects. While it may be disconcerting to an investigator when an intervention yields different results across trials, those are findings to be explored, as opposed to be ignored. Understanding why or how an intervention performed differently across trials is essential information in the service of future intervention development.

As noted, the special issue highlights the benefits of data sharing, as it was the contribution of individual, study-level data that served as the basis for the integrative data analysis paper by Brown et al. 2016. While these investigators initiated sharing on their own, NIMH is proactively attempting to support data sharing through the National Database on Clinical Trials (<https://data-archive.nimh.nih.gov/ndct/>). NIH-wide efforts such as the PhenX Toolkit (<https://www.phenxtoolkit.org/>) provide recommendations for standard measures of phenotypes so that investigators may begin harmonizing measurement strategies, which would facilitate more individual-level integrated data analyses. Hopefully, with new platforms and changing expectations, the culture of sharing data becomes the norm. What may benefit from future consideration would be not just the inclusion of common data elements (CDEs) but also creation of agreed-upon definitions of who is “at-risk.” While CDEs and shared data will vastly improve our capacity to compare findings across studies, outcomes will continue to be difficult to interpret with variability in how risk groups are identified.

NIMH will continue to support the science to enhance our understanding of depression in the hopes that we will eventually achieve our overall institute mission and be able to prevent the onset of mental illness. In pursuit of this goal, we will continue to offer the platforms necessary to facilitate data sharing among investigators, and encourage the focus on understanding mechanism of preventive effects and the need to

look more at common constructs than a diagnostic category. But, irrespective of efforts at the federal level, the most progress will come if the field continues down its own path of sharing and collaboration.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Research Involving Human Participants and/or Animals** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent** N/A

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