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Conducting Psychopathology Prevention Research in the RDoC Era

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Abstract

The Research Domain Criteria (RDoC) initiative promoted by the National Institute of Mental Health emphasizes a dimensional approach to psychopathology that is agnostic to DSM diagnosis. The RDoC project offers exciting possibilities for advancing research aimed at preventing psychopathology. However, prevention has historically been defined using diagnostic status, requiring the field to redefine what constitutes prevention using an RDoC approach. This article outlines new criteria for prevention in the RDoC context and provides guidance for implementing these criteria. We also describe the role of prevention-mechanism trials that examine whether preventive interventions change proximal etiological mechanisms known to be associated with psychopathology. We hope that these modified criteria and recommendations will stimulate new possibilities for prevention research that will advance the field.

Keywords

Keywords: Research Domain Criteria; prevention; mental illness; mental health; risk factor

Conducting Psychopathology Prevention Research in the RDoC Era

The mental health field has a clear interest in pursuing prevention as a way to reduce the burden of mental illness for individuals and society. A decade ago, the Institute of Medicine (IOM) released a report highlighting the importance of prevention research to reduce the risk for mental disorders (Mrazek & Haggerty, 1994). More recently, the American Psychological Association published a series of guidelines to promote prevention efforts among psychologists (American Psychological Association [APA], 2013). Research to date has shown that a number of prevention strategies are effective (e.g., Cuijpers, van Straten, Smit, Mihalopoulous, & Beekman, 2008; Tobler, Roona, Ochshorn, Marshall, Streke, & Stackpole, 2000; Zalta, 2011); however, prevention trials continue to be rare, partially because they demand large, expensive studies that often yield relatively small effects. If we hope for the prevention of psychopathology to become a part of standard mental health care,

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a paradigm shift in conducting prevention research could help to provide a critical platform for invigorating and advancing the field.

The Research Domain Criteria (RDoC) initiative promoted by the National Institute of Mental Health provides an important opportunity to further the science of prevention. The RDoC initiative was developed in response to the increasingly popular view that the categorical-polythetic conceptualization of psychopathology espoused by the *Diagnostic and Statistical Manual (DSM)* and *International Classification of Diseases (ICD)* may not be classifying valid forms of psychopathology (Kendell & Jablensky, 2003). Evidence of this includes the lack of taxonicity observed for these conditions and the large number of individuals who fall below diagnostic cutoffs, but nonetheless are quite impaired (e.g., Haslam, Holland, & Kuppens, 2012; Krueger & Markon, 2006; Shankman, Lewinsohn, Klein, Small, Seeley, & Altman, 2009). Additionally, the assertion that these disorders have unique etiologies is questionable (Krueger & Markon, 2006). An overarching goal of RDoC is to re-conceptualize psychopathology by creating a research framework of dimensional constructs that reflect core mechanisms of psychopathology (Cuthbert & Kozak, 2013; Insel et al., 2010). RDoC constructs make up the ‘rows’ in a two-dimensional matrix often called ‘the RDoC matrix’. The columns of the matrix represent the units (or levels) of analysis. To date, seven units have been proposed - genes, molecules, cells, neural circuits, physiology, behaviors, and self-reports. Additionally, RDoC proponents argue for the importance of using multiple units of analysis in a single study to operationalize the constructs. Thus, rather than conceptualizing a construct such as “potential threat” in terms of one measure (e.g., behavior avoidance of an unpredictable threat), an RDoC study might measure “potential threat” with behavioral, fMRI, physiological (e.g., startle) and self-report measures (Patrick et al., 2013). The RDoC framework is also agnostic about current disorder categories and thus RDoC constructs are viewed as dimensions that cut across traditional diagnostic boundaries. The ultimate hope of the RDoC initiative is to yield a system that will help researchers develop treatments that target underlying etiological mechanisms (Cuthbert, 2014; Cuthbert & Kozak, 2013).

There are several reasons why prevention research would benefit from an RDoC approach. First, preventive interventions have their effects by acting on risk and resilience mechanisms that determine whether an individual develops psychopathology. These interventions are likely to produce greater benefits if their success is based on how they affect underlying mechanisms rather than symptom clusters that fail to map on to important etiological processes. Second, the RDoC initiative emphasizes an exploration of etiological mechanisms across disorders. It is well known that mental disorders often share underlying risk and resilience processes (Kendler, 2012). Targeting common mechanisms with preventive interventions will increase the likelihood of reducing overall impairment due to psychopathology. Third, the RDoC initiative highlights the fact that dysfunction often occurs along a continuum. Traditionally, prevention efforts have focused on whether or not people develop a subsequent diagnosis. This approach undermines the potential benefit of reducing the severity or chronicity of subsequent illness. This is especially detrimental given that the presence or absence of a mental disorder diagnosis does not necessarily align with level of impairment (Shankman, Klein, Lewinsohn, Seeley, & Small, 2008).

Although the RDoC agenda could greatly benefit the science of prevention, it also poses a critical challenge to prevention research. Namely, the RDoC framework is agnostic to mental disorder diagnoses whereas prevention research has historically been defined by categorical diagnostic status. In the IOM reports (Mrazek & Haggerty, 1994; National Research Council and Institute of Medicine [NRC and IOM], 2009), preventive interventions are 1) administered to individuals without a current mental disorder diagnosis and 2) evaluated based on whether they reduce the incidence (new cases) of mental disorders (or delay the onset of mental disorders). These interventions are further categorized into three types based on the target population: 1) universal interventions - administered to all members of a given population, 2) selective interventions - administered to individuals who are at greater risk for developing a disorder, and 3) indicated interventions - administered to individuals with subclinical symptoms of a disorder who do not meet full diagnostic criteria. Thus, both the inclusion/exclusion criteria (the study population) and outcome criteria (what determines if prevention is successful) for prevention research are dependent on categorical mental health diagnoses. This means that advancing prevention research using an RDoC approach demands a rescripting of what constitutes prevention. The more recent 2009 IOM report made a step in this direction by discussing “mental health promotion” (which implies a more dimensional framework) and encouraging preventive interventions that target risk factors for multiple disorders. Yet the IOM report still relied on diagnostic status as a key ingredient for defining prevention. This article outlines a new approach to defining preventive interventions and provides recommendations for approaches to prevention research in the RDoC context.

Defining prevention in the RDoC context

One of the main issues in conducting prevention research with an RDoC lens is how psychopathology is conceptualized. The seemingly simple question of ‘what is psychopathology?’ does not have a uniform answer in the field. For example, some have argued that there are no defining properties of psychopathologies, but rather, they are ‘Roschian concepts’ or prototypes with fuzzy boundaries (Lilienfeld & Marino, 1999). Others have disagreed with this conceptualization (Wakefield, 1999). Relatedly, many researchers have shown that many (if not most) psychopathologies are continuous rather discrete in nature (Krueger & Markon, 2006; Markon, Chmielewski, & Miller, 2011). A detailed discussion of these issues is beyond the scope of this paper. However, these debates have direct implications for prevention research as it is difficult to design a study to prevent something that is ill-defined or defined by individuals differently.

Nevertheless, if the field of prevention science is going to progress and incorporate RDoC, specific guidelines are needed. In this next section, we outline below a set of criteria to re-define what constitutes a preventive intervention in the context of the RDoC initiative (see Table 1 for a summary). This includes new inclusion/exclusion criteria that describe the target population, as well as new outcome criteria that establish the extent to which the intervention was successful. We argue that an intervention trial must satisfy the criteria for both inclusion/exclusion and outcome to be considered a preventive intervention.

Inclusion/Exclusion criteria—According to the IOM, preventive interventions other than universal interventions must target individuals without a clinically diagnosable mental

disorder. This is seen as an important divide because people who receive an intervention for a current diagnosis are viewed as receiving treatment, not prevention. We agree that the goal of prevention is not to reduce a pathology[1] that is already *fully* manifested. Rather, the goal is to ensure that a pathology does not develop or if the pathology does develop, then the extent of the pathology (severity, chronicity, etc…) is mitigated to a clinically meaningful degree. This means that the *exclusion criteria* for preventive interventions must be set to ensure that the pathology is not currently present in its full expression.

For constructs that can be divided into meaningful categories this criterion is clear (e.g., substance abuse prevention for young children who have never used illicit substances). However, establishing a meaningful exclusion cutoff for truly continuous constructs is challenging. The first way to ensure that this criterion could be met is to require that the target problem be within the normal range. For example, if a researcher is doing a prevention trial on anxiety, they could ensure that the sample is within one standard deviation of the mean of the general population in terms of symptom severity, duration, and frequency (assuming that the distributions for the anxiety measures are normally distributed in the population). An alternative approach would be to ensure that individuals' current manifestation of the problem is below an established “tipping point” (Cuthbert & Insel, 2013). Tipping points refer to points along a continuum that mark a meaningful transition to a more severe pathology or behavior. For example, Mausbach et al. (2011) identified a particular cutoff score on a measure of communication and other skills that has strong specificity and sensitivity at predicting whether individuals with schizophrenia can live independently and hold employment. As another example, Mitchell, Tynes, Umaña-Taylor, and Williams (2015) found that youth who experienced 7 or more non-victimization types of adversity had significantly higher depression scores than those with any other number of adversities (and those with fewer than 7 did not differ from each other). This suggests that 7 adversities can be used as a tipping point to determine inclusion criteria for a prevention study.

It is also possible that several tipping points may be present along a single dimension. For example, on a particular dimension, there may be a tipping point that reliably predicts treatment seeking and another than predicts hospitalization. In this case, any one of these tipping points could be used to establish the inclusion criteria. Of course, any tipping points that are utilized should be determined empirically with techniques such as taxometrics analysis (Waller & Meehl, 1998) or based on the separation of clinically meaningful points.

Although the concept of identifying relevant tipping points is promising, it is also the case that some truly continuous constructs may not have tipping points (Haslam et al., 2012). Unlike the DSM, which divides individuals into those with or without a disorder, many proponents of RDoC conceptualize psychopathology continuously, suggesting that everyone has some form of the pathology to a certain extent. This means that researchers will have to select reasonable but arbitrary cutoffs to define whether or not the individual is currently exhibiting the pathology that they are intending to prevent against. This is a common

[1]We use the term “pathology” throughout this manuscript to refer to any physical or mental issue that leads to some impairment (broadly defined) for which a psychosocial treatment would be employed.

practice in prevention studies in medicine. For example, in a meta-analysis of whether blood pressure lowering medications prevented coronary heart disease, the authors noted that the definition of 'high blood pressure' varied across studies a great deal (Law, Morris, & Wald, 2009), suggesting that researchers' exclusion criteria were, to a certain extent, arbitrary. This also applies for psychopathologies. Although some psychopathologies may not be continuous (e.g., schizotypy; Linscott, 2013), the vast majority are (Haslam et al., 2012). In sum, if the underlying distribution of the target pathology is truly continuous, then researchers will have to acknowledge and accept that the criteria set for excluding individuals with full-blown pathology will be arbitrary and may blur the lines between prevention and treatment.

In addition to establishing the exclusion criteria for what constitutes prevention (e.g., excluding those with pathology), the IOM has also proposed several *inclusion criteria* that describe how the sample is selected. As noted above, the IOM has described three inclusion criteria to define types of preventive interventions (Mrazek & Haggerty, 1994; NRC and IOM, 2009): 1) universal interventions - administered to all members of a given population, 2) selective interventions - administered to individuals who are at greater risk for developing a disorder, and 3) indicated interventions - administered to individuals with subclinical symptoms of a disorder who do not meet full diagnostic criteria.

We believe that it is meaningful to distinguish between different inclusion criteria because this may affect the intervention outcome. However, in the context of RDoC, the lines between selective interventions and indicated interventions become blurred as constructs that were previously considered to be risk factors (e.g., biomarkers) may be defined as indicators of pathology according to RDoC. For example, using the IOM system, selecting individuals on the RDoC domain of low reward sensitivity could be considered either selective intervention (e.g., low reward sensitivity is a risk factor for a separate pathology that occurs later) or an indicated intervention (e.g., low reward sensitivity is part of the pathology itself). Thus, we have modified the inclusion criteria to refer to risk based selection on external/contextual constructs and internal/RDoC constructs as described below.

Based on these considerations, we have developed the following exclusion and inclusion criteria for RDoC-based preventive interventions:

A. Exclusion criteria for non-universal interventions

- **i.** *Within the normal range* – This (ultimately arbitrary) criterion is likely to be most relevant when population norms are available. For example, individuals within 1 standard deviation of an IQ of 100 are within the normal range.
- **ii.** *Below an arbitrarily selected cutoff* – This criterion is likely to be most relevant when the underlying distribution of the pathology is continuous and normal. In this case, researchers would either use a construct with a known, normative distribution, or may wish to conduct two-part studies in which an initial sample is used to map the distribution and a cutoff is set based on this distribution (e.g., below the first quartile).

iii. *Below a tipping point* – This criterion is likely to be most relevant when the underlying distribution of the target pathology is not normally distributed and/or continuous. This includes categorical phenomenon.

B. Inclusion criteria

i. *Universal Intervention – all individuals in a group regardless of risk*. In the proposed scheme, universal interventions are equivalent to universal interventions as defined by the IOM. This approach is most beneficial for the delivery of preventive interventions that are relevant for a large portion of the population. This intervention approach is likely to be particularly relevant in the context of RDoC as these interventions could be beneficial to an individual regardless of their degree of pathology. Note that universal interventions do not need to meet the exclusion criteria described above.

ii. *Selective Intervention – individuals in a high-risk group based on external/contextual constructs*. External/contextual risk factors refer to environmental factors, factors outside of the individual, and factors that impact the individuals' social/cultural context. These include demographic variables (e.g., sex, ethnicity, marital status, socioeconomic status), developmental / life events (e.g., rearing practices, divorce, loss), family history (e.g., psychopathology, trauma), and the physical environment (e.g., neighborhood safety, hazardous chemicals).

iii. *Indicated Intervention – individuals in a high-risk group based on the individual's internal/RDoC constructs*. Internal/RDoC factors refer to characteristics of the individual as described in the proposed RDoC matrix (e.g., reward anticipation as measured by physiology, attentional bias to potential threat). This criterion is mostly likely to be used to select individuals who are in a prodromal phase of psychopathology development (if there is a demarcation from non-disorder to disorder).

iv. *Selective-Indicated Intervention – individuals in a high-risk group based on both external/contextual and internal/RDoC constructs*. It is possible that individuals may be selected into a prevention study based on both external/contextual constructs and internal/RDoC constructs (e.g., selecting individuals based on a physiological reward processing *who also* experienced a traumatic event). This prevention type is likely to be particularly relevant for risk groups based on gene by environment interactions.

Outcome criteria—According to the IOM, preventive interventions are successful when they reduce the incidence (new cases) of a disorder or delay the onset of a disorder. Redefining the outcome criteria for prevention in an RDoC context requires a shift away from diagnostic status as the relevant indicator of psychopathology and a shift towards psychological and biological constructs that represent markers of mental illness and mental health. As described above, some of these markers may be truly categorical in nature or may have empirically-based tipping points that indicate meaningful cut points along a dimension.

In these cases, more traditional definitions of outcome can be used that focus on the presence or absence of the pathology as the relevant measure of outcome.

However, many important indicators, particularly neurobiological indicators, are likely to be continuous dimensions with no clear tipping point for analysis (e.g., ventral striatum response to rewards is likely continuous and probably does not have a tipping point). Moreover, RDoC is based on the concept that no one unit of analysis will fully capture the nature of a given pathology. The RDoC initiative therefore encourages the use of multiple units of analysis to define constructs for study. Thus, the ideal outcome variable would likely be represented as a latent factor with multiple indicators that rely on different assessment approaches.

In these cases, investigators should establish whether the future manifestation of the pathology is reduced to a clinically-meaningful degree. As it stands, the majority of existing preventive interventions for psychopathology have assessed whether future symptoms are reduced rather than the extent to which the incidence of the disorder is reduced (e.g., Horowitz & Garber, 2006; Zalta, 2011). Researchers should therefore consider using measures of clinical significance to quantify change such as the Reliable Change Index (Jacobson & Truax, 1991) – a measure computed by dividing the difference between the posttreatment and pretreatment scores by the standard error of the difference between the two scores. RCIs can be used for both single measure variables as well as latent variables from RDoC studies that use multiple indicators of a construct.

These metrics all utilize the degree of the pathology itself to establish outcome. Other outcomes of interest are measures of etiological risk and resilience mechanisms that affect the development of psychopathology. To date, these important outcomes have been largely overlooked in prevention studies. Preventive interventions have their effects by impacting etiological processes that contribute to or buffer against the development of pathology (i.e., reducing causal risk factors and increasing causal resilience factors). Thus, the underlying etiological processes that are targeted by preventive interventions should be considered important outcomes. This is particularly relevant in the RDoC context because multiple forms of pathology often share underlying etiological processes (e.g., attentional biases contribute to both depression and anxiety). We refer to interventions that focus on etiological processes as outcomes as *"prevention-mechanism" trials*.

These prevention-mechanism trials are an important addition to preventive intervention research because they allow for an examination of proximal mechanisms. This approach may be more cost-efficient as they can be done using smaller samples. That is, the effect on a proximal outcome is likely to have a higher effect size than an effect on a more distal outcome, requiring a smaller N. Moreover, it is noteworthy that a prevention-mechanism approach is consistent with the current NIH proposal for how to conduct clinical trials (Insel, 2013) and existing prevention approaches in medicine. For example, knowing that condom use prevents against a host of sexually-transmitted illnesses (STIs), preventive interventions have used the outcome variable "rate of condom use" as the outcome variable of interest rather than merely assessing rates of STIs (e.g., Foss, Hossain, Vickerman, & Watts, 2007). Some studies in the mental health field have already begun to take this approach. For

example, a meta-analysis by Stice and colleagues (2007), examined the extent to which preventive interventions for eating pathology alter key risk factors including thin-ideal internalization, body dissatisfaction, and dieting.

Despite the promise of prevention-mechanism research, there are several important limitations to this approach that are important to consider. First, for mental illness and mental health, etiological mechanisms are often more difficult to establish than etiological mechanisms for physical illness and injury. Moreover, even when etiological mechanisms are established, they often have poor penetrance or a weak impact on the ultimate expression of psychopathology. For example, the links between smoking and lung disease or antibodies and the flu are much stronger than the links between rumination and depression (Nolen-Hoeksema, 2000) or amygdala-frontal connectivity and anxiety (Kim et al., 2011). This is because etiological mechanisms for psychopathology are often highly multifactorial in nature. As a result, a prevention-mechanism trial may demonstrate the ability to modify a risk mechanism, but the modification of this mechanism may not necessarily translate to the prevention of psychopathology. Investigators should be mindful of these limitations when using a prevention-mechanism approach by focusing on factors with stronger penetrance and assessing multiple purported etiological mechanisms within a single study.

Based on these considerations, we have outlined below a revised set of outcome criteria for preventive interventions in the context of RDoC (Romano & Hage, 2000). Additionally, we have defined the criteria for a new set of interventions termed prevention-mechanism interventions. Notably, these interventions must be conducted with an appropriately selected sample based on the inclusion / exclusion criteria described above to be considered prevention or prevention-mechanism interventions.

A. Outcome criteria for preventive interventions

i. *Stops pathology from occurring*. This criterion should largely be used for mental illness and mental health outcomes that are truly categorical in nature such as suicide attempts or re-hospitalization. This criterion can also be applied to continuous constructs in which important tipping points have been identified or to arbitrarily selected cutoffs for phenomena with normal distributions. These cutoffs should be pre-determined prior to the study initiation and should be linked to the relevant inclusion criteria.

ii. *Delays the onset of pathology*. This criterion focuses on delaying the onset of a problem that is categorical in nature or that has a relevant tipping point / cutoff. This criterion should largely be applied to behaviors in which developmental timing is a critical aspect of risk for psychopathology-related impairment. For example, delaying first use of alcohol in youth can reduce risk of alcohol-related impairment (McGue, Iacono, Legrand, Malone, & Elkins, 2006).

iii. *Reduces the pathology and/or increases emotional well-being to a clinically-meaningful degree.* This criterion should largely be used for continuous measures of mental illness and mental health. As noted above, investigators should consider using a latent variable approach in which multiple units of

analysis are used as indicators to establish the extent of pathology or wellness.

B. Outcome criteria for prevention-mechanism interventions

i. *Reduces factors that contribute to pathology or strengthens factors that protect against pathology*. This criterion focuses on causal risk and resilience factors as the outcome of interest. These constructs should be well-established as causal factors and must be malleable to represent outcomes of interest. For example, the RDoC construct of circadian rhythms (measured via EEG, self-report, and prolactin levels) could be an outcome variable for a prevention-mechanism trial given its association with risk for bipolar disorder (Alloy, Nusslock, & Boland, 2015).

ii. *Strengthens factors that promote emotional well-being*. Compared to the other prevention-mechanism criteria, which focus on avoiding disease, this criterion emphases ways to improve well-being by enhancing factors that promote general mental health. Although promoting well-being will likely reduce risk for psychopathology, the goal of promoting positive mental health is viewed as an important goal in itself (World Health Organization, 2001). Moreover, there are likely to be some factors for which their presence promotes well-being but their absence does not necessarily promote psychopathology (e.g., frequent experiences of gratitude).

Implementing the revised criteria

There are several considerations that researchers should take into account in implementing these revised criteria for conducting “RDoC-ian” prevention studies. Given that prevention-mechanism trials have not been expressly elaborated before, it is important to consider the necessary conditions for this research approach to be successful. The first important issue is that prevention-mechanism studies must be linked with well-established mechanism research in order to determine potential preventive effects. This means that it is important to first demonstrate that the target mechanism is indeed a *causal* risk factor for the outcome of interest.

Once a mechanism of outcome has been established (e.g., condom use → decreased incidence of STI; sleep-wake cycle disruption → bipolar mood disturbance), a prevention-mechanism study can be used to test whether the preventative intervention changes the mechanism (e.g., intervention→increased condom use; intervention → stable sleep-wake cycles). Then, a prevention study can be done to test whether the preventative intervention changes the clinical outcome via the proposed mechanism (e.g., intervention→ increased condom use →decreased STIs; intervention→ stable sleep-wake cycles →decreased bipolar mood episodes). This step-wise approach has advantages to a direct prevention approach in that prevention-mechanism research can identify promising interventions with studies that are less costly, less burdened by concerns of power, and that clearly elaborate the proposed mechanisms of action. However, this approach also rests on having a strong foundation of mechanism research in which causal risk and resilience processes that have a strong connection to psychopathology are reliably identified. The field has identified some of these

processes, but their specificity and sensitivity to various pathologies have not been firmly established (although it is possible that many of these processes are critical mechanisms for multiple pathologies). Thus, further research is needed to establish causal risk factors to develop effective prevention-mechanism and prevention research.

It is also important to note that although the inclusion/exclusion criteria and outcomes described above are at the individual level, prevention-mechanism and prevention research could be implemented on the community level (families, neighborhoods, etc.) as well. The role of community level variables have not been discussed a great deal in papers on RDoC, but are nonetheless important to the initiative (Shankman & Gorka, in press). For example, researchers could do a community-based prevention study with the ultimate goal of reducing bullying in schools by examining the effect of an intervention on the RDoC domain of impulsivity. Additionally, impulsivity could be measured either at the individual level or perhaps at the community level, such as aggregative impulsive tendencies at the classroom, school, or neighborhood level.

Lastly, there are several issues that should be highlighted related to the point that RDoC studies typically conceptualize constructs (mechanisms, outcomes, etc.) dimensionally. First, the psychopathology dimension does not only have to be the number of symptoms at a given point in time. While this is an important dimension, a preventive intervention say for depression could have the goal of reducing the length of depressive episodes - particularly given that the chronicity of depression is as important (if not more important) than the severity of symptoms at one point in time (Klein, 2008). Second, it is important to note that many dimensional constructs are not necessarily unipolar in nature such that one end of the dimension is advantageous and the other end of the dimension is pathogenic. Rather, for many dimensions, having an extreme response on either side is related to dysfunction. For example, extreme inhibition is associated with social anxiety (Lorian & Grisham, 2010) whereas extreme disinhibition is associated with substance use (Leeman, Hoff, Krishnan-Sarin, Patock-Peckham, & Potenza, 2014). Thus, there may be relevant tipping points or markers of pathology on either side of some dimensional scales. This means that in some instances, the goal of preventive interventions may be to help people move towards the middle of these dimensions rather than towards one end or the other.

Limitations of an RDoC approach to prevention

Redefining prevention research using an RDoC approach holds promise for advancing the science of prevention and ultimately reducing the burden of mental illness. However, the definitions proposed in this article have several limitations and raise several issues that must be considered.

First, the RDoC matrix is designed to be an ever-evolving and growing list of constructs and units of analysis to measure those constructs. This may make it difficult or worrisome for researchers to engage in longitudinal prevention trials as the specific target (or indicator of the target) may change after the study was begun.

Second, as discussed above, how psychopathology is conceptualized (e.g., continuous vs. discrete, normally distributed in the population vs. non-normal, etc…) has direct

implications for conducting prevention studies. Unfortunately, given that RDoC is explicitly agnostic towards how psychopathology is conceptualized (Cuthbert, 2014), it is up to the researcher to define (and justify) their definition of psychopathology.

Third, some investigators are likely to be uncomfortable with the lack of a clear prevention-treatment divide using this new approach. One major concern is that an overly inclusive definition for prevention research may dilute resources for prevention research. Indeed, there has been a long-standing struggle in defining prevention (NRC and IOM, 2009), especially since treatment for one disorder may constitute prevention of a comorbid disorder or certain problem behaviors (e.g., treating major depression may prevent comorbid substance use disorders, [Curry et al., 2012]). Moreover, individuals that potentially meet diagnostic status have always comprised part of the sample in universal prevention approaches.

We can attempt to increase our certainty that we are engaging in prevention by limiting the sample to those with little or no impairment due to psychopathology or selecting a universal sample in which we expect a largely non-impaired group. Although the proposed criteria may further blur the lines between prevention and treatment, it is arguable that the overly stringent criteria set forth by the IOM has somewhat hampered prevention research by requiring large and expensive trials to demonstrate prevention effects. It is our hope that by taking the proposed approach, greater resources will be directed towards prevention mechanism trials that are more cost-effective and will ultimately lead to more effective preventive interventions that are designed to target underlying risk and resilience processes.

A final limitation of this approach is the subsequent translation and dissemination of research findings to clinical practice, which continues to rely on diagnostic status for intervention delivery. This is of course a concern related to the RDoC initiative more broadly – although RDoC is only proposed at this point to be a research initiative, not a practice one. Prevention work cannot only exist in the context of grant-funded research if it hopes to have a larger impact on mental illness in our society. Thus, researchers will need to consider strategies for marketing preventive interventions and describing the cost-savings of prevention outside of its impact on diagnosis. To do so, researchers should include important outcome measures that can clearly be linked to functional outcomes that have an associated cost (e.g., work days lost). Ideally, these outcome measures should be standardized across studies using common data elements to more easily make comparisons across trials.

Conclusions

Although the mental health field has had a long-standing interest in pursuing prevention research, progress in this area has been slow and limited in scope. The IOM criteria for what constitutes prevention requires large and expensive trials, which is likely to hinder progress in this field. The RDoC initiative offers an important platform for advancing prevention research by focusing on altering underlying dimensions of pathology that cut across disorders rather than reducing the incidence of a specific cluster of symptoms that may not be a valid representation of underlying etiology. This article outlines a series of criteria and recommendations for how to pursue prevention research in the context of RDoC. These modified criteria are not without limitations and require thoughtful application, just as the previous approach. However, we hope that these new recommendations will stimulate a new

wave of prevention research that will have a meaningful impact on reducing the burden of mental illness.

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Table 1
Proposed criteria for prevention research in the RDoC context

Criteria	Definition
Exclusion Criteria	For selecting a target population without fully manifested psychopathology
Within the normal range	Study population does not have fully manifested psychopathology based on the fact that all participants are within the population norm
Below a tipping point	Study population does not have fully manifested psychopathology based on the fact that all participants are below an empirically-established tipping point
Below an arbitrarily selected cutoff	Study population does not have fully manifested psychopathology based on the fact that all participants are below an arbitrarily selected cutoff
Inclusion Criteria	For selecting a target population based on level of risk
Universal intervention*	Selects all individuals in a group regardless of risk
Selective intervention	Selects individuals in a high-risk group based on external/contextual constructs
Indicated intervention	Selects individuals in a high-risk group based on internal/RDoC constructs
Selective-Indicated intervention	Selects individuals in a high-risk group based on both external/contextual and internal/RDoC constructs
Outcome Criteria for preventive intervention	For measuring preventive intervention success
Stops psychopathology from occurring	Intervention is successful based on the fact that psychopathology does not occur (categorical construct), remains below a pre-determined tipping point (dimensional construct), or remains below a pre-determined arbitrarily selected cutoff (dimensional construct)
Delays the onset of psychopathology	Intervention is successful based on the fact that the full manifestation of psychopathology is delayed in onset
Reduces the pathology and/or increases emotional well-being to a clinically-meaningful degree	Intervention is successful based on the fact that psychopathology is reduced to a clinically-meaningful degree or emotional well-being is increased to a clinically-meaningful degree (relative to a control group)
Outcome Criteria for prevention-mechanism intervention	For measuring prevention-mechanism intervention success
Reduces factors that contribute to pathology or strengthens factors that protect against pathology	Intervention is successful based on the fact that well-established causal risk factors for psychopathology are reduced or well-established causal resilience factors for psychopathology are enhanced
Strengthens factors that promote emotional well-being	Intervention is successful based on the fact that well-established causal factors that promote mental health are enhanced

Note. A study must satisfy at least one of the exclusion criteria, at least one of the inclusion criteria and at least one of outcome criteria to qualify as a preventive intervention or prevention-mechanism trial with the exception that exclusion criteria do not apply to universal interventions*.