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## Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review

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### Abstract

**Background:** Clinical evidence has long suggested there may be heterogeneity in the patterns and predictors of common mood and anxiety disorders; however, epidemiologic studies have generally treated these outcomes as homogenous entities. The objective of this study was to systematically review the epidemiologic evidence for potential patterns of heterogeneity of common mood and anxiety disorders over the lifecourse in the general population.

**Methods:** We reviewed epidemiologic studies examining heterogeneity in either the nature of symptoms experienced ("symptom syndromes") or in patterns of symptoms over time ("symptom trajectories"). To be included, studies of syndromes were required to identify distinct symptom subtypes, and studies of trajectories were required to identify distinct longitudinal patterns of symptoms in at least three waves of follow-up. Studies based on clinical or patient populations were excluded.

**Results:** While research in this field is in its infancy, we found growing evidence that, not only can mood and anxiety disorders be differentiated by symptom syndromes and trajectories, but that the factors associated with these disorders may vary between these subtypes. Whether this reflects a causal pathway, where genetic or environmental factors influence the nature of the symptom or trajectory subtype experienced by an individual, or whether individuals with different subtypes differed in their susceptibility to different environmental factors, could not be determined. Few studies addressed issues of comorbidity or transitions in symptoms between common disorders.

**Conclusion:** Understanding the diversity of these conditions may help us identify preventable factors that are only associated with some subtypes of these common disorders.

## Background

Numerous large epidemiologic surveys have demonstrated the high prevalence of mood and anxiety disorders among the general population. The recent World Health Organization (WHO) World Mental Health Surveys, for example, interviewed 60,463 community-based adults living in 14 countries. These studies estimated the 12 month prevalence of mood disorders in developed countries at between 3.1 percent in Japan and 9.6 percent in the US, and the prevalence of anxiety disorders at between 5.3 percent and 18.2 percent [1]. The US National Comorbidity Replication found lifetime prevalence estimates for these conditions of 20.8 percent for mood disorders and 28.8 percent for anxiety disorders [2]. These high prevalence estimates are associated with a heavy burden on the health of the community, with most individuals categorized with a disorder having clinically significant symptoms and suffering a significant associated disruption to their daily life [3]. According to 2004 estimates from the WHO, neuropsychiatric disorders are the leading cause of disability among non-communicable conditions worldwide [4].

Clinical experience has long suggested that mood and anxiety disorders are heterogeneous syndromes that vary markedly between individuals with respect to their clinical presentations, responses, longitudinal course, and risks of recurrence. According to Thase (2007), for example, the origins of the atypical depressive subtype can be traced back to the work of Sir Aubrey Lewis, who in the 1930s proposed dividing depression into endogenous or nonendogenous subtypes, a partition supported by the psychopharmacologic work of West and Dally in 1959 [5]. In 1982, Sheehan and Sheehan similarly proposed an alternative classification scheme for phobic disorders based on the presence or absence of endogenous anxiety symptoms; the two subgroups differed with respect to their clinical presentation, response to treatment, and longitudinal course [6]. Prospective work has shown that patients with mood and anxiety disorders follow different longitudinal trajectories that vary in terms of age or onset, symptom severity, and risks of recurrence [7-11]. For example, in a prospective study of 120 patients treated for current major depressive disorder, Ceroni and colleagues (1984) found that the majority of patients recovered within the first few months of treatment, but 39 percent were persistently depressed during the first year of follow-up [8]. Additionally, in a prospective study of 83 moderate to severely depressed patients, 20 percent were almost entirely free of depressive symptoms over ten years of follow-up, while 5 percent were continuously depressed [7].

The modern paradigm for the diagnosis of mental disorders is based on the classification systems of the DSM and ICD. Accordingly, most recent population-based research


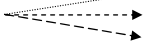
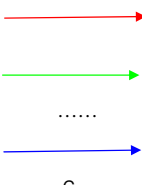
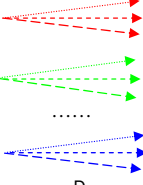
has used different survey instruments to define the presence of mood and anxiety disorders based on these criteria, either in the form of a categorical diagnosis or as symptom severity levels on a unidimensional scale. These approaches have greatly increased our understanding of these disorders and identified a range of risk factors for new onsets [12-14]. However, failing to account for heterogeneity in the clinical presentations of mood and anxiety disorders comes at a cost. If, for example, a specific risk factor was only associated with a particular subtype of a disorder, this may be overlooked in an analysis investigating all mood disorders as the outcome; there is some evidence to suggest this may be the case [15]. Incomplete understanding of the specific etiologic pathways that manifest in distinct phenotypes has important implications for the translation of research into effective treatment and clinical management [16]. This is only one of several criticisms levied against current models of classification in a growing appeal for a new taxonomy that appreciates the heterogeneous nature of mood and anxiety disorders highlighted by earlier clinical work [17-19].

Facilitated by methods such as latent class analysis, a growing body of epidemiologic research has attempted to disentangle phenotypic heterogeneity of common mood and anxiety disorders by identifying clusters of symptoms. Consistent with extant clinical and population-based research, we propose that potential patterns of heterogeneity can be categorized as relating to clusters of symptoms, according to clinical features or severity ("symptom syndromes"), and patterns of symptoms over time ("symptom trajectories"). Figure 1 summarizes the potential patterns of heterogeneity of symptom syndromes and trajectories of common mood and anxiety disorders observed. It is the goal of this paper to systematically review the epidemiologic evidence for potential patterns of heterogeneity in both the symptom syndromes and in the trajectories of common mood and anxiety disorders. We restricted our review to population-based studies, as studies of the life course of these disorders need to include the large number of individuals with significant symptoms who do not seek appropriate clinical care and who would be excluded from studies drawn only from clinical populations [20]. It is hoped that this review will be useful in pointing the way to further research and potentially to more effective intervention strategies.

## Methods

### Selection criteria

The sampling frame for this review included population-based studies that assessed the heterogeneity of symptom syndromes or trajectories of common mood and anxiety disorders. We restricted our review to psychiatric definitions of common mood and anxiety disorders and, as such, these disorders were selected based on the taxon-

		HETEROGENEITY IN TRAJECTORIES	
		NO (N=1)	YES (N=X, where X>1)
HETEROGENEITY IN SYMPTOM SYNDROMES	NO (N=1)	 A.	 B.
	YES (N= Y, where Y>1)	 C.	 D.

**Figure 1**  
**Potential patterns of heterogeneity in symptom syndromes and trajectories of common mood and anxiety disorders.** Notes: A. represents homogeneity; B. represents the X potential phenotypes resulting from heterogeneity of trajectories but not symptom syndromes; C. represents the Y potential phenotypes resulting from heterogeneity of symptom syndromes but not trajectories; D. represents the X\*Y potential phenotypes resulting from heterogeneity of both symptom syndromes and trajectories.

omy of the DSM-IV [21]. We also based our review on DSM-IV definitions of mood and anxiety disorders because most studies assessing heterogeneity in these conditions appeared in the peer-reviewed literature after 1994, the year the DSM-IV was published, and also because we wanted to minimize the extent to which heterogeneity in the symptom syndromes or trajectories of common mood and anxiety disorders was an artifact of changing nosology over time. Studies of the heterogeneity of symptom syndromes were required to identify distinct symptom subtypes. Studies of the heterogeneity of trajectories were required to identify distinct longitudinal patterns of symptoms, or the characteristics of these trajectories, in at least three waves of follow-up. Studies based on samples recruited from clinical settings (e.g., inpatients or outpatients) were excluded.

**Search strategy**

We obtained papers for this review using a four-step procedure. First, because our review was based on DSM-IV definitions of the mood and anxiety disorders, we performed a systematic search of the peer-reviewed literature using the Index Medicus and ISI Web of Knowledge databases. We identified potential studies for inclusion by

querying all possible search fields for combinations of the following terms: 'anxiety', 'mood', 'disorder', 'heterogeneity', 'symptom', 'subtype', 'symptom subtype', 'trajectory', 'trajectories', 'depression', 'posttraumatic stress', 'PTSD', 'obsessive', 'compulsive', and 'ADHD'. Second, we analyzed abstracts for all studies identified and excluded papers that did not satisfy selection criteria. Third, we analyzed the full-text version of all remaining studies and excluded those that did not satisfy selection criteria. Fourth, we retrieved articles not identified by our literature review from the references of remaining papers and excluded those that did not satisfy selection criteria.

**Search results**

Our search identified 521 papers, 46 of which satisfied selection criteria. In Table one and Table two (Additional files 1 and 2), we present all findings within two broad categories according to whether they assessed heterogeneity of symptom syndromes (n = 17) or heterogeneity of trajectories (n = 29), respectively. Within each table, studies were further stratified based on the particular mood and anxiety disorder assessed (e.g., depression, posttraumatic stress disorder) and then sorted in ascending order based on the age group of the sample (i.e., adolescent, adult, elderly) and alphabetically based on the first author's last name. Each table provides a summary of the sample, the sample size, the authors, and the study design in the first column, the age group of the sample in the second column, the timeframe of interviews in the third column, and the main findings in the fourth column. These tables aim to highlight the most meaningful conclusions from the studies collected.

**Results**

**Heterogeneity in symptoms of mood and anxiety disorders**

We identified 17 studies that evaluated heterogeneity in symptoms of mood and anxiety disorders (Additional file 1). Of the 17 studies, 10 studies assessed depression, three studies assessed social phobia, and there was one study each on PTSD, ADHD, bipolar disorder, and panic attack. One study focused on adolescents, 15 on adult samples, and one on elderly adults. Fifteen of 17 studies were cross-sectional. Seven of 17 studies distinguished clinical subtypes of bipolar disorder, depression, and panic attack based on definitions specified *a priori*. Ten studies relied on different statistical methods, most frequently latent class analysis, to identify subtypes based on observed data.

**Evidence for distinct symptom subtypes**

Eleven of the 17 studies focused on the identification of distinct clinical subtypes of mood and anxiety disorders. For depression, two general population samples [22,23] and two samples of twins from population-based registries [24,25] separated adults into latent classes based on

their symptom patterns. In their general population sample of adults from Baltimore, Chen and colleagues (2000) identified five latent classes with distinct patterns of depressive symptoms, including non-depressed, anhedonic, suicidal, psychomotor, and severely depressed subtypes [23]. Using latent class analysis, Sullivan and colleagues (1998) identified six patterns of depressive symptoms in a probability sample of the US population, including a severe typical subtype with a high lifetime occurrence of depressive symptoms, a severe atypical subtype with many depressive symptoms and symptoms characterized by appetite increase and weight gain, and four other subtypes of varying symptom severity [22]. Similarly, two twins studies using latent class analysis, including a study of female-female twin pairs [25] and a study of male-male and male-female twin pairs [24], identified a severe typical depressive subtype where nearly all criteria for major depression were met, an atypical depressive subtype where participants commonly endorsed symptoms of depressed mood, loss of interest and/or pleasure, and increased appetite and weight gain, and five additional subtypes varying according to their patterns and degree of classical depressive symptoms. In contrast to these results demonstrating subtypes of symptom syndromes of depressive disorders, a study of elderly adults found little evidence for a clinically defined vascular subtype of depression in the general populations of Amsterdam and Rotterdam [26].

Four studies attempted to identify subtypes of social phobia [27-30]. In a general population sample of adults from Sweden, Furmark and colleagues (2000) found evidence of severe, intermediate, and mild subtypes that were distinguished by the symptom severity of their social phobia [27]. In contrast, a study using principal components analysis found that the number of social fears in their sample of young German women was distributed continuously with no clear evidence for distinct symptom subtypes based on the number of symptoms of social phobia [30]. In a latent class analysis that assessed clusters of symptoms patterns, Kessler and colleagues (1998) identified a subtype that endorsed few symptoms of social phobia, a subtype characterized by fears related to social speaking, and a subtype with multiple speaking and non-speaking fears in the general population of the US [28]. Two other studies provided evidence that those with social phobia characterized by only speaking-related fears may represent a distinct subtype from those with non-speaking social fears [28-30].

There was one study each on posttraumatic stress disorder (PTSD) and attention-deficit/hyperactivity disorder (ADHD). Using a taxometric analysis, Waelde and colleagues (2005) found evidence of a dissociative subtype of PTSD among Vietnam theater era veterans that was char-

acterized by a higher prevalence of symptoms of dissociation, PTSD, and dysthymia [31]. In a latent class analysis of adolescent female twins aged 13 to 23 years, three ADHD subtypes of clinical interest, among nine total subtypes, were identified, including an inattentive subtype without comorbidity, an inattentive subtype with increased symptoms of oppositional defiant disorder (ODD), and a combined inattentive/hyperactive-impulsive subtype with elevated levels of ODD, separation anxiety and depressive symptoms [32].

#### *Factors associated with symptom subtypes*

Thirteen studies assessed whether specific characteristics might be associated with subtypes of common mood and anxiety disorders. Two studies comparing the class assignment of twins showed that monozygotic twins were more likely to be assigned to the same latent subtypes of depression and ADHD than dizygotic twins [24,32], suggesting a potential genetic influence on class membership. Two general population samples showed that personal and familial characteristics discriminated between latently defined subtypes of depression [22,23]. For example, a study of Baltimore adults showed that a family history of depression was associated with membership in the anhedonic, psychomotor, suicidal, and severely depressed subtypes, female gender was associated with the suicidal and several depressed subtypes, and exposure to stressful life events was associated with psychomotor and suicidal subtypes [23]. Sociodemographic factors, including levels of income, educational attainment, and social support also distinguished between subtypes of social phobia. In general, subtypes characterized by greater symptom severity or functional impairment, including those with both speaking and non-speaking social fears relative to those with only speaking fears [30], were associated with lower levels of income, education, and social support than milder subtypes [27,28]. A number of studies showed that comorbid anxiety, mood, and substance disorders were more common among some depressive [22,33] and panic [34] subtypes than others. For example, one study showed the atypical major depression subtype was associated with an increased prevalence of comorbid panic disorder and drug abuse/dependence [33], whereas a national sample of US adults showed that more deviant personality and attitudes, increased psychiatric comorbidity, and parental alcohol/drug use were associated with membership in severe typical or atypical depressive classes relative to milder subtypes [22]. Three studies estimated the prevalence of diagnostically defined seasonal subtypes of depression and bipolar disorder [35-37]; two of these studies investigated the influence of environmental factors, but found no association between the latitude of a participants' household dwelling in Ontario and the prevalence of the seasonal subtypes of depression [36] or bipolar disorder [35]. A few studies compared the course

of depressive subtypes. For example, one study of young adults from Zurich showed that the course of diagnostically defined atypical depression was associated with an earlier age of onset and greater chronicity [38].

### **Heterogeneity in the trajectories of mood and anxiety disorders**

Of the 29 studies that assessed heterogeneity in the trajectories of mood and anxiety disorders (Additional file 2), 22 assessed depression, three assessed anxiety, two assessed general anxiety and depression, one assessed symptoms of hyperactivity, and one assessed PTSD. Fifteen studies focused on children, adolescents, or young adults, eight on adults, five on elderly adults, and one on a sample of mixed age groups. Studies applied different statistical techniques, most commonly latent growth curve or semi-parametric group-based modeling, to identify trajectories of mood and anxiety disorders on the basis of the observed data.

#### *Evidence for distinct trajectories*

Six studies identified distinct longitudinal trajectories of depressive symptoms among children, adolescents, or young adults [39-45]. For example, in a semi-parametric group-based analysis of early adolescents from North-western Quebec, Brendgen and colleagues (2005) identified consistently low, moderate, increasing, and consistently high trajectories of depression; almost 50 percent of participants were in the consistently low group [39]. Additionally, a study of African American adolescents from a mid-Western city who were at risk of high school dropout identified consistently high, consistently low, increasing, and decreasing depressive trajectories [41]. Most recently, Costello and colleagues (2008) identified four trajectories of depression in a nationally representative sample of 12 to 25 years olds; 29 percent were assigned to the group without depressed mood, 59 percent were assigned to the stable low depressed mood, 10 percent were assigned to the declining depressed mood group, and two percent were assigned to the late escalating depressed mood group [45]. Three studies assessed depressive trajectories among adults, including two studies of caregivers [46-48]. Using a semi-parametric group-based analysis, Campbell and colleagues (2007) identified low-stable, moderate-stable, intermittent, moderate-increasing, high-decreasing, and high-chronic patterns of depressive symptoms among mothers as their children aged from one month to seven years, with more than 80 percent of mothers in the low-stable or moderate-stable trajectory groups [46]. A latent state-trait analysis of elderly residents from the Baltimore area found that heterogeneity in depressive symptoms was accounted for by two factors, a highly heritable trait effect that reflects underlying vulnerability and a residual state effect that reflects occasion specific circumstances [49]. Six trajectory groups, including two asymptomatic groups, a stable low-

depressed group, an emerging depressive symptoms group, a remitting depressive symptoms group, and a persisting depressive symptoms group, were identified in a community sample of elderly adults from rural south-western Pennsylvania [50].

Two studies used semi-parametric group-based models to identify distinct trajectories of symptoms of anxiety among children. In a representative sample of children from Quebec, Duchesne and colleagues (2008) identified low, moderate, high, and chronic trajectories of symptoms of anxiety [51]. A study of boys enrolled in the WIC program in Pittsburgh also identified four trajectories of symptoms of anxiety, including low, low-increasing, high-declining, and high-increasing groups [52]. In contrast to the Quebec study, where 40 percent of the sample was assigned to the high severity group, 50% of boys from Pittsburgh were assigned to the low anxiety trajectory. Additionally, two studies examined heterogeneity in the trajectories of both mood and anxiety disorders. A sample of 4,627 members of the 1946 British birth cohort were followed from age 13 through 53, with 44.8 percent considered to have no symptoms, 33.6 percent having repeated minor or moderate symptoms generally below threshold of mental illness, 11.3 percent having few symptoms in adolescence but minor or moderate symptoms in adulthood, 5.8 percent having symptoms in adolescence but not in adulthood, 2.9 percent having few symptoms in adolescence but severe symptomatology in adulthood, and 1.7 percent having persistent or repeated severe symptoms [53]. In a representative sample of adults from Zurich, Merikangas and colleagues (2003) used log-linear models to investigate the relation between anxiety, depression, and comorbid anxiety and depression. This study showed that comorbid anxiety and depression was more stable over time than either anxiety or depression alone and that transitions from anxiety only to depression only were common, whereas transitions from depression only to anxiety only were rare [54].

One study used semi-parametric group-based models to assess heterogeneity in the trajectories of hyperactivity symptoms; in that study, four trajectories of symptoms, including very low, low, moderate, and high groups, were identified in a nationally representative sample of Canadian children [55]. With regards to PTSD, a study of Army personnel who returned from the Gulf War used growth mixture modeling to identify two trajectories of post traumatic stress disorder; 57 percent of participants were assigned to the first group, which had lower post traumatic stress disorder symptomatology at baseline and showed slight increases over time, and 43 percent of participants were assigned to the second group, which had higher levels of initial symptoms and a significant increase over time [56].

#### *Factors associated with distinct trajectories*

17 studies assessed the correlates of distinct depressive trajectories among children, adolescents, and young adults. Trajectories of depressive symptoms [39-41,44,57-60] and symptoms of anxiety [61] have been frequently shown to differ by gender. For example, some studies showed that female gender was associated with membership in more severely depressed groups [39,41]. Other work showed that girls' depressive symptoms increased through early and middle adolescence while boys' symptoms remained relatively constant [57,58]; differential exposure to stressful life events may explain observed gender differences in depressive trajectories [58].

Besides demographic factors such as age, family characteristics, emotional and personality traits, sociodemographic factors, performance in school, substance abuse and other comorbidities, and exposure to stress, stressful life events, and negative life events were commonly associated with adverse symptom trajectories of anxiety, depression, and hyperactivity in children and adolescents [41-45,52,55,57-59,61]. Characteristics of parents, including maternal prenatal smoking, maternal depression, and hostile parenting practices, were associated with more symptomatic trajectories of anxiety and hyperactivity among children and adolescents [52,55]. Sociodemographic factors, including non-white race/ethnicity and lower socioeconomic status were associated with membership in depressed mood trajectory groups relative to groups without symptoms of depression [45]. Several studies showed that poorer performance in school was associated with greater severity of depressive symptoms [41,42,59]; for example, a study of African American adolescents from a mid-Western city found that adolescents who presented with consistently high levels of depressive symptoms were more likely to have lower grade point averages compared with adolescents in other groups [41]. Comorbidities, including adolescents' smoking, alcohol consumption, and illicit drug use [42,45,60], poorer social relationships among adolescents, particularly with their parents and same sex peers [39,59], and greater parental educational attainment have also been associated with more adverse adolescent depressive symptoms trajectories [59]. Conversely, social supports and marriage were associated with lower levels of depressive symptoms among young adults in a Western Canadian city [59].

Six studies assessed the determinants of distinct depressive trajectories among adults, with many examining the influence of socioeconomic circumstances. In a study of Southeast Asian refugees in Vancouver more economically integrated refugees showed higher initial levels of subclinical depressive symptomatology, but greater declines over time [62]. In a study of mothers followed from one month to seven years after the birth of their

child, greater educational attainment and a higher income to needs ratio, among other factors, were associated with low-stable levels of depression relative to more severe depressive trajectories [46]. Similarly, Li (2005) found that while wife and daughter caregivers with higher incomes were more likely to exhibit a downward trajectory of depressive symptoms that began before their care recipients died, caregivers with lower incomes and caregivers of recipients with more problematic behaviors were slower to recover after recipients died [63]. In contrast to these results, a US national study of 3,617 adults did not find a difference in trajectory between high and low income groups, although there was divergence over time between college graduates and those with less than a high school diploma [64].

The most commonly studied determinant of depressive trajectories among the elderly has been stress. Using a probability sample of 1,972 Black and White adults age 65 and older from five counties in North Carolina, a significant association was found between stress growth and growth of depressive symptoms, particularly among Blacks [65,66]. On the other hand, a study of community-dwelling adults aged 65 and older from areas of North Carolina showed that the positive relation between age and depressive symptoms was driven primarily by differences between cohorts, and that adjustment for indicators of the life course (i.e., marriage, socioeconomic status, employment status), physiological declines, and sex compositions largely explained these cohort effects [67].

Only single studies have examined determinants in the trajectories of either PTSD or mood and anxiety disorders combined among adults. For PTSD, White Army personnel returning from the Gulf War and those with higher educational attainment and less combat exposure had a lower likelihood of reporting high levels of posttraumatic stress symptoms [56]. Among the participants from the 1946 British birth cohort, lower birthweight, older age at first standing, female gender, and manual social class were associated with more severe trajectories of anxiety and depressive symptoms [53].

#### **Discussion**

While only a limited amount of work has been conducted in this field, we found growing epidemiologic evidence that, not only can mood and anxiety disorders be differentiated by symptom syndromes and trajectories, but that the factors associated with these disorders may vary between these subtypes.

Most population-based epidemiologic research investigating heterogeneity in the symptom syndromes of common mood and anxiety disorders has focused on major depressive disorder, with only sparse work relating to ADHD,

bipolar disorder, panic attack, PTSD, or social phobia. This work suggests that depression may not be a homogeneous disorder characterized by a single phenotype (Figure 1A), but a heterogeneous constellation of potentially distinct subtypes of symptom syndromes (Figure 1C). For depression, the syndromic subtype most commonly identified in this review was atypical depression, a subtype defined by symptoms including increased appetite and weight gain and greater chronicity. Although the validity of atypical depression has been debated since the subtype was codified in the DSM-IV in 1994 [5,68,69], three latent class analyses provided support for an atypical subtype that was distinct in terms of its patterns and severity of symptoms [22,24,25]. However, these analyses did not support the presence of mood reactivity as a necessary symptom for the diagnosis of atypical depression, a finding corroborated by recent clinical work [69]. There was less evidence for other clinical subtypes of depression, including melancholic, seasonal, and vascular depression [26,36,37]. For example, an anhedonic latent class exhibiting a greater loss of interest was identified by one study [23]; however, other work showed that these symptoms were non-specific [24]. Additional epidemiologic replication of these clinical subtypes is needed. Additionally, although cross-sectional and longitudinal research has identified high rates of comorbidity of mood and anxiety disorders, few studies of symptom syndromes explored symptoms of more than one disorder. These are some of the limitations that will have to be addressed for a new typology to emerge.

Familial aggregation studies suggest that heterogeneity in the symptom syndromes of depression and ADHD are partly explained by genetic similarities [24,32]. However, the particular genetic, sociodemographic, psychological, social, or environmental characteristics that explain observed heterogeneity in symptoms is unclear; many of these characteristics may lie along the same etiologic pathway. Future research will have to address a number of issues. First, because most studies were cross-sectional and started in adulthood, it was impossible to distinguish associations that may reflect a causal pathway from those that may be spurious. Longitudinal assessments that establish a temporal structure between risk factor and phenotype will help to understand observed associations. Second, most of the associations between exposures and subtypes were non-specific in nature. For example, analysis of the National Comorbidity Survey showed that depressive atypicality, a subtype based on patterns of symptoms, was associated with interpersonal dependency, reduced self esteem and stressful life events [22,24]. Similarly, analysis of symptom subtypes in the Baltimore Epidemiologic Catchment Area study found more severe subtypes were associated with female gender and family history but not stressful life events, while mild or moderate cases were associated with family history and stressful

events, but not female gender [23]. Although it is plausible that one exposure may be associated with multiple subtypes, further phenotypic characterization of these disorders will increasingly help disaggregate these relations and facilitate identification of the specific genetic, personal, and social factors associated with distinct symptom subtypes [16].

We found strong evidence of heterogeneity in the longitudinal trajectories of common mood and anxiety and disorders. There are three potential explanations for these patterns. First, heterogeneity in trajectories may be the result of having distinct symptom subtypes in the population, each of which may have a distinct longitudinal course (Figure 1C). In this case, heterogeneity in symptom syndromes may be spuriously confused as heterogeneity in the longitudinal trajectories of mood and anxiety disorders. Second, there may be true intra-individual heterogeneity in the longitudinal course of a single clinical disorder because of differential exposure to genetic, personal, or environmental factors. Therefore, a homogeneous clinical disorder may present as multiple phenotypes (Figure 1B). Third, there may be intra-individual heterogeneity in the longitudinal course of multiple symptom subtypes (Figure 1D). Overall, our review found stronger evidence for intra-individual heterogeneity in the longitudinal course of a single disorder than heterogeneity resulting from having distinct clinical subtypes in the population. Several studies conducted among children and adolescents found evidence of distinct depressive trajectories characterized by different levels of symptom severity. In general, the most prevalent trajectories were stable patterns of consistently low to moderate levels of symptoms [39,40,42,45]; however, up to one-quarter of some samples were assigned to classes characterized by persistent levels of severe symptomatology [42,43].

Only sparse research has investigated intra-individual heterogeneity in the longitudinal course of multiple symptom subtypes. In that study, Angst and colleagues (2002) found that atypical depression was characterized by greater longitudinal chronicity [38]. Studies that examined trajectories of mood and anxiety disorders combined were also very limited, although both clinical and epidemiologic evidence suggests that many individuals experience frequent transitions between symptoms of these disorders over time. It is possible that individuals who experience symptoms of both disorders over a lifetime share characteristics that distinguish them from individuals who only experience symptoms of one specific disorder. This seems an area worthy of further investigation.

There was strong evidence that a variety of factors experienced over the lifecourse, ranging from personal to social, may influence trajectories of common mood and anxiety disorders. There was also evidence to suggest that vulner-

ability to external factors may vary between individuals with differing trajectories. Extended longitudinal studies starting in childhood are needed to distinguish between these effects. The extant literature suggests that certain characteristics may predispose individuals to membership in more severe, versus less severe, longitudinal trajectories of depression. For example, among children, adolescents, and young adults, female gender, poorer school performance, greater exposure to stressful life events, and comorbidities including substance use were all associated with trajectories characterized by greater depressive symptomatology [41-44,57-60]. Similarly, among adults, increased demands among caregivers were associated with more severe depressive trajectories [63]. Conversely, a number of studies suggest that certain factors, particularly greater access to social and material resources, may act as buffers and predispose individuals to less severe trajectories of depression. Among adolescents and young adults, research showed that stronger social relationships and greater access to social supports predicted membership in trajectories characterized by less severe symptoms of depression [39,59]. Furthermore, one study showed that greater parental educational attainment was associated with a steeper decline in adolescents' depressive symptoms [59], suggesting that socioeconomic status may be associated with less severe depressive trajectories. Among adults, greater educational attainment and financial resources were associated with less severe depressive trajectories [46,63]. As with symptom syndromes, whether environmental factors are the cause of a particular trajectory, or whether individuals with a genetic predisposition to a particular trajectory are more susceptible to specific environmental factors, can only be answered by extended longitudinal studies and the assessment of interaction between genetic and environmental factors [70,71]

Finally, an alternative way of viewing these patterns was proposed by twin studies and the Baltimore Longitudinal Study of Aging, which both support a trait-state model of depression, where symptom levels can be accounted for by two factors: a level (average or "trait") effect that is highly heritable and reflects underlying vulnerability and a residual ("state") effect that is non-inheritable and reflects occasion specific circumstances [49,71]. In this theoretical framework, trajectory subtype may be considered a manifestation of trait effects. These studies concluded that attempts to identify environmental determinants of symptoms of depression might best focus on *deviations* about average levels over multiple assessments.

#### **Methodological challenges**

Further inference about the heterogeneity in symptom subtypes and trajectories of common mood and anxiety disorders over the lifecourse is limited by a number of methodological issues. First, the studies included in this

review were population-based and utilized a variety of diagnostic survey instruments that are, to varying degrees, imperfect substitutes for clinician-administered structured interviews. Error in the measurement of the mood and anxiety disorders may influence the validity of individual studies and complicate comparisons between studies. Further information on the validity of common diagnostic instruments can be found elsewhere [72]. Second, in most studies that assessed the characteristics associated with distinct clinical presentations or trajectories, methods of variable selection were not theoretically predicated. This makes it difficult to assess whether a particular characteristic was associated with heterogeneity in mood and anxiety disorders across studies. A multilevel framework for understanding how factors experienced over the life course influence the heterogeneity of common mood and anxiety disorders may facilitate model specification and improve comparability between studies. Third, studies used a number of different methods for defining subtypes. Studies that assessed heterogeneity of clinical presentations either specified criteria *a priori* or used statistical methods to identify subtypes. In general, disorders recognized as distinct clinical entities by the DSM-IV, including seasonal and atypical depression, were more likely to rely on definitions specified *a priori* than less commonly studied subtypes. The dichotomy between pre-defined and empirically derived subtypes represents a bias-variance trade-off. While having pre-defined criteria facilitates comparisons between studies, there is ongoing debate about the validity of recognized subtypes [73,74]. On the other hand, methods such as latent class analysis are more flexible and permit investigation of the number and nature of underlying subgroups in a sample [75,76]. However, these techniques can be overly sensitive to the data and may complicate comparisons across studies. For example, are the mild depressive classes from two different studies qualitatively similar [22,25]? This trade-off was not relevant when considering studies assessing heterogeneity in trajectories of mood and anxiety disorders. These studies typically used latent class growth, semi-parametric group-based modeling, or other techniques to identify distinct trajectories according to the inferential goal of the analysis [77,78]. Fourth, despite the clinical and epidemiologic evidence for frequent comorbidity and transitions between mood and anxiety disorders, more than 90 percent of the studies identified by our review assessed symptoms of depression alone. Comorbidity with, and transitions between, these disorders is likely to be a field particularly worthy of further investigation. Finally, most studies did not distinguish between age and cohort effects.

#### **Conclusion**

This is the first review to explore the epidemiologic evidence for heterogeneity of mood and anxiety disorders. Clinical experience suggests these common conditions



vary markedly between individuals, and the limited epidemiologic studies conducted in this area are consistent with these observations. This is important since this research also suggests that the factors associated with these disorders may vary by symptom and trajectory subtype. These associations may be overlooked in epidemiologic studies that consider these outcomes as homogeneous entities. Understanding the diversity of these conditions may help us identify preventable factors that are only associated with some subtypes of these common disorders. This knowledge may aid the development of more effective treatment interventions.

### Abbreviations

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; PTSD: posttraumatic stress disorder; ADHD: attention-deficit/hyperactivity disorder; ODD: oppositional defiant disorder

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

All authors contributed equally to the conception of the study, the interpretation of results, and the drafting of the manuscript. AN was responsible for the acquisition of data. All authors read and approved the final manuscript.

### Additional material

#### Additional file 1

**Table one.** Key studies assessing heterogeneity of symptom syndromes of common mood and anxiety disorders.

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#### Additional file 2

**Table two.** Key studies assessing heterogeneity of trajectories of common mood and anxiety disorders.

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### References

- Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, et al: **Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys.** *Jama* 2004, **291(21)**:2581-2590.
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE: **Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.** *Archives of general psychiatry* 2005, **62(6)**:593-602.
- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE: **Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.** *Archives of general psychiatry* 2005, **62(6)**:617-627.
- World Health Organization: **The global burden of disease: 2004 update.** Geneva, Switzerland: World Health Organization Press; 2008.
- Thase ME: **Recognition and diagnosis of atypical depression.** *The Journal of clinical psychiatry* 2007, **68(Suppl 8)**:11-16.
- Sheehan DV, Sheehan KH: **The classification of phobic disorders.** *International journal of psychiatry in medicine* 1982, **12(4)**:243-266.
- Nyström S: **Depression: factors related to 10-year prognosis.** *Acta psychiatrica Scandinavica* 1979, **60(2)**:225-238.
- Berti Ceroni G, Neri C, Pezzoli A: **Chronicity in major depression. A naturalistic prospective study.** *Journal of affective disorders* 1984, **7(2)**:123-132.
- Robins E, Guze SB: **Classification of affective disorders – The primary-secondary, the endogenous-reactive and neurotic-psychotic concepts.** In *Recent Advances in Psychobiology of the Depressive Illness* Edited by: Williams TA, Katz MM, Shields JA. London: Government Printing Office; 1972:283-293.
- van Weel-Baumgarten E, Bosch W van den, Hoogen H van den, Zitman FG: **Ten year follow-up of depression after diagnosis in general practice.** *The British journal of general practice* 1998, **48(435)**:1643-1646.
- Takahashi S, Nakamura M, Iida H, Iritani S, Fujii M, Yamashita Y, Yoichi I: **Prevalence of panic disorder and other subtypes of anxiety disorder and their background.** *Japanese journal of psychiatry and neurology* 1987, **41(1)**:9-18.
- Brugha TS: **The effects of life events and social relationships on the course of major depression.** *Current psychiatry reports* 2003, **5(6)**:431-438.
- de Graaf R, Bijl RV, Ravelli A, Smit F, Vollebergh WA: **Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study.** *Acta psychiatrica Scandinavica* 2002, **106(4)**:303-313.
- Perkonig A, Kessler RC, Storz S, Wittchen HU: **Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity.** *Acta psychiatrica Scandinavica* 2000, **101(1)**:46-59.
- Chen LS, Eaton WW, Gallo JJ, Nestadt G, Crum RM: **Empirical examination of current depression categories in a population-based study: symptoms, course, and risk factors.** *The American journal of psychiatry* 2000, **157(4)**:573-580.
- Hasler G, Drevets WC, Manji HK, Charney DS: **Discovering endophenotypes for major depression.** *Neuropsychopharmacology* 2004, **29(10)**:1765-1781.
- Krishnan KR: **Towards a scientific taxonomy of depression.** *Dialogues in clinical neuroscience* 2008, **10(3)**:301-308.
- Parker G: **Through a glass darkly: the disutility of the DSM nosology of depressive disorders.** *Canadian journal of psychiatry* 2006, **51(14)**:879-886.
- Parker G: **Classifying depression: should paradigms lost be regained?** *American journal of psychiatry* 2000, **157(8)**:1195-1203.
- Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM: **Prevalence and treatment of mental disorders, 1990 to 2003.** *The New England journal of medicine* 2005, **352(24)**:2515-2523.
- APA: *Diagnostic and statistical manual of mental disorders* fourth edition. Washington, DC: American Psychiatric Association; 1994.
- Sullivan PF, Kessler RC, Kendler KS: **Latent class analysis of lifetime depressive symptoms in the national comorbidity survey.** *The American journal of psychiatry* 1998, **155(10)**:1398-1406.
- Chen L, Eaton WW, Gallo JJ, Nestadt G: **Understanding the heterogeneity of depression through the triad of symptoms, course and risk factors: a longitudinal, population-based study.** *Journal of affective disorders* 2000, **59(1)**:1-11.
- Sullivan PF, Prescott CA, Kendler KS: **The subtypes of major depression in a twin registry.** *Journal of affective disorders* 2002, **68(2-3)**:273-284.
- Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC: **The identification and validation of distinct depressive syn-**

- dromes in a population-based sample of female twins. *Archives of general psychiatry* 1996, **53(5)**:391-399.
26. Naarding P, Tiemeier H, Breteler MM, Schoevers RA, Jonker C, Koudstaal PJ, Beekman AT: **Clinically defined vascular depression in the general population.** *Psychological medicine* 2007, **37(3)**:383-392.
  27. Furmark T, Tillfors M, Stattin H, Ekselius L, Fredrikson M: **Social phobia subtypes in the general population revealed by cluster analysis.** *Psychological medicine* 2000, **30(6)**:1335-1344.
  28. Kessler RC, Stein MB, Berglund P: **Social phobia subtypes in the National Comorbidity Survey.** *The American journal of psychiatry* 1998, **155(5)**:613-619.
  29. Stein MB, Deusch R: **In search of social phobia subtypes: Similarity of feared social situations.** *Depression and anxiety* 2003, **17(2)**:94-97.
  30. Vriends N, Becker ES, Meyer A, Michael T, Margraf J: **Subtypes of social phobia: Are they of any use?** *Journal of anxiety disorders* 2007, **21(1)**:59-75.
  31. Waelde LC, Silvern L, Fairbank JA: **A taxometric investigation of dissociation in Vietnam veterans.** *Journal of traumatic stress* 2005, **18(4)**:359-369.
  32. Neuman RJ, Heath A, Reich W, Bucholz KK, Madden PAF, Sun L, Todd RD, Hudziak JJ: **Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins.** *Journal of child psychology and psychiatry, and allied disciplines* 2001, **42(7)**:933-942.
  33. Horwath E, Johnson J, Weissman MM, Hornig CD: **The validity of major depression with atypical features based on a community study.** *Journal of affective disorders* 1992, **26(2)**:117-125.
  34. Goodwin RD, Hamilton SP, Milne BJ, Pine DS: **Generalizability and correlates of clinically derived panic subtypes in the population.** *Depression and anxiety* 2002, **15(2)**:69-74.
  35. Schaffer A, Levitt AJ, Boyle M: **Influence of season and latitude in a community sample of subjects with bipolar disorder.** *Canadian journal of psychiatry* 2003, **48(4)**:277-280.
  36. Levitt AJ, Boyle MH: **The impact of latitude on the prevalence of seasonal depression.** *Canadian journal of psychiatry* 2002, **47(4)**:361-367.
  37. Levitt AJ, Boyle MH, Joffe RT, Bauml Z: **Estimated prevalence of the seasonal subtype of major depression in a Canadian community sample.** *Canadian journal of psychiatry* 2000, **45(7)**:650-654.
  38. Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K: **Toward validation of atypical depression in the community: results of the Zurich cohort study.** *Journal of affective disorders* 2002, **72(2)**:125-138.
  39. Brendgen M, Wanner B, Morin AJ, Vitaro F: **Relations with parents and with peers, temperament, and trajectories of depressed mood during early adolescence.** *Journal of abnormal child psychology* 2005, **33(5)**:579-594.
  40. Dekker MC, Ferdinand RF, van Lang ND, Bongers IL, Ende J van der, Verhulst FC: **Developmental trajectories of depressive symptoms from early childhood to late adolescence: gender differences and adult outcome.** *Journal of child psychology and psychiatry, and allied disciplines* 2007, **48(7)**:657-666.
  41. Repetto PB, Caldwell CH, Zimmerman MA: **Trajectories of depressive symptoms among high risk African-American adolescents.** *Journal of adolescent health* 2004, **35(6)**:468-477.
  42. Rodriguez D, Moss HB, Audrain-McGovern J: **Developmental heterogeneity in adolescent depressive symptoms: associations with smoking behavior.** *Psychosomatic medicine* 2005, **67(2)**:200-210.
  43. Stoolmiller M, Kim HK, Capaldi DM: **The course of depressive symptoms in men from early adolescence to young adulthood: identifying latent trajectories and early predictors.** *Journal of abnormal psychology* 2005, **114(3)**:331-345.
  44. Wiesner M, Kim HK: **Co-occurring delinquency and depressive symptoms of adolescent boys and girls: a dual trajectory modeling approach.** *Developmental psychology* 2006, **42(6)**:1220-1235.
  45. Costello DM, Swendsen J, Rose JS, Dierker LC: **Risk and protective factors associated with trajectories of depressed mood from adolescence to early adulthood.** *Journal of consulting and clinical psychology* 2008, **76(2)**:173-183.
  46. Campbell SB, Matestic P, von Stauffenberg C, Mohan R, Kirchner T: **Trajectories of maternal depressive symptoms, maternal sensitivity, and children's functioning at school entry.** *Developmental psychology* 2007, **43(5)**:1202-1215.
  47. Taylor DH, Ezell M, Kuchibhatla M, Ostbye T, Clipp EC: **Identifying trajectories of depressive symptoms for women caring for their husbands with dementia.** *Journal of the American Geriatrics Society* 2008, **56(2)**:322-327.
  48. Zhang BH, Mitchell SL, Bambauer KZ, Jones R, Prigerson HG: **Depressive symptom trajectories and associated risks among bereaved Alzheimer disease caregivers.** *American journal of geriatric psychiatry* 2008, **16(2)**:145-155.
  49. Davey A, Halverson CF Jr, Zonderman AB, Costa PT Jr: **Change in depressive symptoms in the Baltimore longitudinal study of aging.** *The journals of gerontology* 2004, **59(6)**:P270-277.
  50. Andreeescu C, Chang CC, Mulsant BH, Ganguli M: **Twelve-year depressive symptom trajectories and their predictors in a community sample of older adults.** *International psychogeriatrics* 2008, **20(2)**:221-236.
  51. Duchesne S, Vitaro F, Larose S, Tremblay RE: **Trajectories of anxiety during elementary-school years and the prediction of high school noncompletion.** *Journal of youth and adolescence* 2008, **37(9)**:1134-1146.
  52. Feng X, Shaw DS, Silk JS: **Developmental trajectories of anxiety symptoms among boys across early and middle childhood.** *Journal of abnormal psychology* 2008, **117(1)**:32-47.
  53. Colman I, Ploubidis GB, Wadsworth ME, Jones PB, Croudace TJ: **A longitudinal typology of symptoms of depression and anxiety over the life course.** *Biological psychiatry* 2007, **62(11)**:1265-1271.
  54. Merikangas KR, Zhang H, Avenevoli S, Acharyya S, Neuenchwander M, Angst J: **Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study.** *Archives of general psychiatry* 2003, **60(10)**:993-1000.
  55. Romano E, Tremblay RE, Farhat A, Cote S: **Development and prediction of hyperactive symptoms from 2 to 7 years in a population-based sample.** *Pediatrics* 2006, **117(6)**:2101-2110.
  56. Orcutt HK, Erickson DJ, Wolfe J: **The course of PTSD symptoms among Gulf War veterans: a growth mixture modeling approach.** *Journal of traumatic stress* 2004, **17(3)**:195-202.
  57. Ge X, Lorenz FO, Conger RD, Elder GH, Simons RL: **Trajectories of stressful life events and depressive symptoms during adolescence.** *Developmental psychology* 1994, **30(4)**:467-483.
  58. Ge X, Natsuaki MN, Conger RD: **Trajectories of depressive symptoms and stressful life events among male and female adolescents in divorced and nondivorced families.** *Development and psychopathology* 2006, **18(1)**:253-273.
  59. Galambos NL, Barker ET, Krahn HJ: **Depression, self-esteem, and anger in emerging adulthood: seven-year trajectories.** *Developmental psychology* 2006, **42(2)**:350-365.
  60. Needham BL: **Gender differences in trajectories of depressive symptomatology and substance use during the transition from adolescence to young adulthood.** *Social science & medicine* (1982) 2007, **65(6)**:1166-1179.
  61. Hale WW, Raaijmakers Q, Muris P, van Hoof A, Meeus W: **Developmental trajectories of adolescent anxiety disorder symptoms: A 5-year prospective community study.** *Journal of the American Academy of Child and Adolescent Psychiatry* 2008, **47(5)**:556-564.
  62. Wickrama KA, Beiser M, Kaspar V: **Assessing the longitudinal course of depression and economic integration of south-east Asian refugees: an application of latent growth curve analysis.** *International journal of methods in psychiatric research* 2002, **11(4)**:154-168.
  63. Li LW: **From caregiving to bereavement: trajectories of depressive symptoms among wife and daughter caregivers.** *The journals of gerontology* 2005, **60(4)**:P190-198.
  64. Kim J, Durden E: **Socioeconomic status and age trajectories of health.** *Social science & medicine* (1982) 2007, **65(12)**:2489-2502.
  65. George LK, Lynch SM: **Race differences in depressive symptoms: a dynamic perspective on stress exposure and vulnerability.** *Journal of health and social behavior* 2003, **44(3)**:353-369.
  66. Lynch SM, George LK: **Interlocking trajectories of loss-related events and depressive symptoms among elders.** *The journals of gerontology* 2002, **57(2)**:S117-125.
  67. Yang Y: **Is old age depressing? Growth trajectories and cohort variations in late-life depression.** *Journal of health and social behavior* 2007, **48(1)**:16-32.

68. Lam RW, Stewart JN: **The validity of atypical depression in DSM-IV.** *Comprehensive psychiatry* 1996, **37(6)**:375-383.
69. Seemuller F, Riedel M, Wickelmaier F, Adli M, Mundt C, Marneros A, Laux G, Bender W, Heuser I, Zeiler J, et al.: **Atypical symptoms in hospitalised patients with major depressive episode: frequency, clinical characteristics, and internal validity.** *Journal of affective disorders* 2008, **108(3)**:271-278.
70. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, et al.: **Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene.** *Science* 2003, **301(5631)**:386-389.
71. McGue M, Christensen K: **The heritability of depression symptoms in elderly Danish twins: occasion-specific versus general effects.** *Behavior genetics* 2003, **33(2)**:83-93.
72. Eaton WW, Hall AL, Macdonald R, McKibben J: **Case identification in psychiatric epidemiology: a review.** *International Review of Psychiatry* 2007, **19(5)**:497-507.
73. Magnusson A: **An overview of epidemiological studies on seasonal affective disorder.** *Acta psychiatrica Scandinavica* 2000, **101(3)**:176-184.
74. Hansen V, Skre I, Lund E: **What is this thing called "SAD"? A critique of the concept of Seasonal Affective Disorder.** *Epidemiologia e psichiatria sociale* 2008, **17(2)**:120-127.
75. McCutcheon AC: *Latent class analysis* Beverly Hills, CA: Sage; 1987.
76. Hagenars J, McCutcheon AC, (Eds): *Applied latent class analysis models* New York, NY: Cambridge University Press; 2002.
77. Nagin D: **Analyzing developmental trajectories: a semiparametric, group-based approach.** *Psychological methods* 1999, **4(2)**:139-157.
78. Duncan TE, Duncan SC: **An introduction to latent growth curve modeling.** *Behavior therapy* 2004, **35(2)**:333-363.

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