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Highlights:

- Most cases of anxiety disorder onset are preceded by adverse events
- Harm to a family member or friend is the most frequent such precedent
- A strong overall association persists after adjustment for important variables

Abstract

This study tested the hypothesis that adverse events induce anxiety and are associated with increased risk of onset of anxiety disorders. Data from Waves 1 (N=43,093; 2001-2002) and 2 (N=34,653; 2004-2005) of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) were used to assess whether adverse events at baseline are associated with increased risk of anxiety disorder onset over three years of follow up. Sixty-six percent (SE: 1.0) of respondents with an anxiety disorder in the intervening period between Waves 1 and 2 had experienced an adverse life event in the year prior to the Wave 1 interview. In logistic regression models adjusted for sociodemographic and psychiatric characteristics, adverse life events at baseline were associated with anxiety disorder onset within the three-year follow up period. The pattern of association between adverse events and anxiety disorder onset was similar across sub-types, and injury, illness or death of family or close friends consistently had the strongest association with anxiety disorder onset. These findings suggest that adverse life events play a role in the onset of anxiety disorders.

Key words: Anxiety Disorders; Epidemiology; Life Events; Stress; Adversity; Onset; Recurrence

Adverse life events and the onset of anxiety disorders

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1. Introduction

Adverse life events have a well-documented effect on risk for mental disorders, with most research focusing on depression (Kessler, 1997; Paykel and Cooper, 1992) and, by definition, post-traumatic stress disorder (Storr et al., 2012). Anxiety disorders are also a possible result of adverse life events, inasmuch as these events (a) signal the possibility of future repeated exposure to adversity, (b) reduce individuals' capacity to cope with potential threats (Bateson et al., 2011), or (c) provide external verification regarding an individual's coping capabilities (Lazarus, 1991) and therefore give a clearer indication of vulnerability (Bateson et al., 2011). From the perspective of the individual, these might register as: 'this event now seems more likely to happen'; 'this event has made me more vulnerable to future adversity'; or 'I have realised as a result of this event exactly how vulnerable I am'. The tendency to imagine and fixate on the possibility of experiencing adverse future scenarios is a characteristic feature of anxiety (Miloyan et al., 2014), but it remains unclear to what extent the actual experience of adverse events induces anxiety.

Results of previous studies suggest that recent adverse life events are associated with increased risk of anxiety disorder onset (Finlay-Jones and Brown, 1981; Francis et al., 2012; McLaughlin et al., 2010; Taher et al., 2015). Although the results of these studies generally coincide with one another, three of them were based on small, clinical samples and potentially affected by selection bias (Finlay-Jones and Brown, 1981; Francis et al., 2012; Taher et al., 2015). One study assessed the past-year association between adverse life events and mental disorders, conditional on having experienced childhood adversity (McLaughlin et al., 2010), and another attempted to distinguish between depression and anxiety based on blind reviewers' ratings of features of participants' reported adverse events (Kendler et al., 2003).

The current analysis uses the two waves of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) to assess whether self-reported recent adverse life events are associated with increased risk of onset of anxiety disorders. We first describe the relationship between adverse events and anxiety disorders, overall and by sub-type. We then assess whether the presence and frequency of adverse events in the year prior to the baseline interview is associated with increased risk of anxiety disorders at a three-year follow-up interview. Finally, we examine whether the presence of adverse events in the year prior to baseline poses differential risk of first versus recurrent onset of anxiety disorders at follow-up.

1. Method

2.1 Sample

Wave 1 of the NESARC was conducted in a nationally representative sample of 43,093 civilian, non-institutionalized adults, aged 18-98 years, from all 50 U.S. states and the District of Columbia in 2001-2002 (Grant et al., 2003b). Young adults, African-Americans, and Hispanics were purposively oversampled. Face-to-face interviews were conducted by trained lay interviewers using the Alcohol Use Disorder and Associated Disabilities Interview Schedule, DSM-IV version (AUDADIS-IV) (Grant et al., 2003a; Ruan et al., 2008). Wave 2 was conducted in 2004-2005 with 34,653 of the original respondents (Grant and Kaplan, 2005). Of those designated as respondents in wave 1, 81% completed interviews; of these 86.7% completed interviews at Wave 2, resulting in a cumulative response rate of 70.2%.

2.2 Measures and Procedure

Sociodemographic variables included age, sex, education (Bachelor's degree or higher; Associate's degree or some college; completed high school or its equivalent; or did not complete high school); marital status (married or cohabiting; widowed, divorced or separated; never

married) and urbanicity of residence (urban or suburban; rural). The AUDADIS-IV examined a total of 12 stressful life events, and whether these occurred in the year prior to the Wave 1 interview. Six of the 12 events queried were conceptualized as adverse events according to the definition in the present study: (i) illness, injury or (ii) death of any family member or close friend, (iii) having been fired or laid off from one's job, (iv) having separated from a steady relationship or divorced from marriage, (v) having experienced a major financial crisis including bankruptcy or inability to pay bills on time, or (vi) having been (or having a family member who was) the victim of a crime. Among the other six items, three were excluded for not being necessarily adverse (moving; changing jobs; seeking employment), two for referring to perceived stress (trouble with boss or co-worker; trouble with neighbour), and one for lack of specificity (having had, or having a family member who had, trouble with police, arrested, or in jail). The last one is non-specific in that being convicted of a crime could be associated with a lack of anxiety (Marks and Nesse, 1994).

Anxiety disorder diagnoses over the lifetime prior to the Wave 1 interview, and in the intervening period prior to the Wave 2 interview were obtained using the AUDADIS-IV, and included Panic Disorder (with or without Agoraphobia), Social Phobia, Specific Phobia and Generalized Anxiety Disorder. The AUDADIS-IV has fair-to-moderate reliability for lifetime (kappa: 0.42-0.48) and 12-month (kappa: 0.41-0.52) anxiety disorder diagnoses (Grant et al., 2003a). Respondents who screened positive for anxiety disorder in the year prior to the Wave 2 interview, and who had not met diagnostic criteria for anxiety disorder in the year prior to the Wave 1 interview constituted those with anxiety disorder *onset*. Among those with anxiety disorder onset, those who had reported a lifetime history of anxiety disorder over the lifetime prior to the Wave 1 interview, excluding in the year prior to the interview, were defined as having *recurrent onset*. Those who had not reported a lifetime history of anxiety disorder prior to the

Wave 1 interview were defined as having *first onset*. Psychiatric control variables included lifetime diagnoses of mood and substance use disorders.

2.3 Analyses

We estimated the proportion of respondents who reported adverse events in the year prior to the Wave 1 interview, and the percentage of those respondents with anxiety disorder onset by the Wave 2 interview. Logistic regression analyses controlling for age, sex, education, marital status, urbanicity, mood and substance use disorders, and anxiety disorders (excluding in the past-year) at Wave 1 were performed to assess the association of any past-year adverse event at Wave 1 with anxiety disorder onset in the intervening years prior to the Wave 2 interview. In a second model, we replaced the binary measure of adverse events (presence vs. absence) with a frequency measure. We then estimated the frequency and weighted proportion of respondents with first and recurrent onsets of anxiety disorders at Wave 2, followed by logistic regression analyses to assess the association of any past-year adverse event with first and recurrent onsets of anxiety disorder, after adjusting for the aforementioned covariates. We tested the interaction of the risk of first versus recurrent onset of anxiety disorder associated with baseline adverse events by calculating a relative odds ratio. All analyses were performed using Stata 12.0/SE. Probability weights were used to adjust for oversampling, attrition and non-response.

---Insert Table 1 about here---

2. Results

Fifty-seven percent (SE: 0.6) of respondents experienced at least one adverse event in the year prior to the Wave 1 interview (See Table 1). Fewer than 10% of the overall sample experienced three or more adverse events in this period. The majority of respondents with an onset of any anxiety disorder sub-type in the year prior to the Wave 2 interview had experienced at least

one adverse event in the year prior to the Wave 1 interview. After adjusting for sociodemographic and psychiatric variables, having experienced any adverse event in the year prior to the Wave 1 interview (OR: 1.23; 95% CI: 1.11-1.35) was associated with any anxiety disorder in the year prior to the Wave 2 interview (See Table 2). We then substituted the binary variable indicating the presence or absence of adverse life events with a variable indicating the frequency of adverse events, which was also associated with increased risk of anxiety disorder onset at follow up (OR: 1.11; 95% CI: 1.07-1.16).

---Insert Table 2 about here---

The total prevalence of recurrent onset (relapse) of any anxiety disorder (1.3%; SE: .07) was much lower than the total prevalence of first onset (10.7%; SE: 0.2), and this pattern held across all anxiety sub-types (see Table 3). We observed a higher risk of recurrent versus first onset for anxiety disorders, as indicated by the positive coefficient for lifetime history of anxiety disorder at baseline in all of the analyses. In analyses adjusted for sociodemographic and psychiatric characteristics, adverse events were associated with increased risk of first but not recurrent onset of any anxiety disorder (see Table 4). However, the interaction of these estimates (Relative OR: 1.09; 95% CI: 0.84-1.41) suggested that there was no difference in the risk of first versus recurrent onset attributable to adverse events in the year prior to the baseline interview.

---Insert Tables 3 & 4 about here---

It should not be assumed that undesirable events preceded anxiety disorders. Therefore, we assessed whether a lifetime diagnosis of anxiety disorder (excluding 12-month) at baseline was associated with increased risk of experiencing an adverse event in the year prior to the Wave 2 interview. Those with a past-year diagnosis of anxiety disorders were excluded because approximately two-thirds of these cases co-occurred with adverse events in the same year, and

three years may be an insufficient length of time for the adverse event to completely resolve. We did not observe an association between lifetime anxiety measured at baseline and adverse events measured at follow-up (OR: 0.99; 95% CI: .90-1.10).

3. Discussion

The results of this study support the hypothesis that adverse life events are associated with increased risk of onset of anxiety disorders. Adverse events were associated with higher risk of onset of all anxiety sub-types except for Social Phobia, and there was no difference between the risks of first versus recurrent onset. The discussion is structured on three points.

First, most cases of anxiety disorder onset in this study were preceded by adverse events. This finding is consistent with the results of a signal detection approach that predicts that life circumstances that enhance vulnerability to potential threats induce anxiety (Bateson et al., 2011). From this perspective, adverse events play a causal role in inducing states of anxiety inasmuch as such events serve to increase vulnerability in one or more ways, and as such are associated with increased risk of anxiety disorder onset. For example, having experienced a recent financial crisis would leave participants vulnerable to a variety of potential situations (e.g., insufficient funds to cover necessary automobile repairs). The death of a family member or a close friend, or the dissolution of a steady relationship or a marriage can lead to anxiety about what the consequences of this change in circumstances might entail (e.g., lack of social support, challenges to raising children). These findings have practical implications in that individuals who undergo intervention may have adverse life events underlying their clinical presentation, and the extent to which such events (or their implications) remain unresolved at the time of treatment may undermine those efforts.

Prior work has sought to explain associations between adverse life events and depression (Kessler, 1997) and more recently substance use disorders (Keyes et al., 2011). It remains unclear whether the association between adverse life events and mental disorder is accounted for by trait-specific mechanisms (e.g., anxiety or low mood), given the broad associations between adverse events and mental disorders (Boden et al., 2014; Kendler et al., 1999; Lloyd and Turner, 2008; Slopen et al., 2011). It could be that adverse events have a direct influence on the emergence and time-course of some classes of mental disorder symptoms that in turn cause others to arise. For example, it might be that an initial wave of affective symptoms give way to substance use problems (Khantzian, 1985). A more general possibility is that adverse events directly elicit negative emotional states, and that inasmuch as these situations persist, people are likelier to meet criteria for a number of common mental disorders. These observations raise important questions about the relationship between mental disorders and adverse life events. For example, there may be dispositional traits (e.g., rumination, worry) that predispose individuals to respond more poorly to adverse events and develop mental disorders (Ruscio et al., 2015).

A third point pertains to first and recurrent onset of anxiety disorders. Apparently in contrast to previous work suggesting that a history of anxiety disorder may signal poor coping ability (Lazarus, 1991), the finding that there were many more cases of first versus recurrent onset suggest that those with a history of anxiety disorder may frequently learn to cope with adverse events from prior experience. Nonetheless, we did find that the risk of recurrent onset was higher than the risk of first incident onset, and that a lifetime history of major depression posed almost three times the risk of recurrent relative to first onset. It is possible that the subset of the population that experiences recurrent onset may have higher dispositional anxiety or experience chronic life adversities that we were unable to investigate.

This is the first population-based study to directly assess the relationship between adverse life events and the onset of anxiety disorder in terms of anxiety sub-types and first and recurrent onset. The study had several limitations. The first limitation pertains to the low reliability of the anxiety disorder diagnoses in the AUDADIS-IV. The second pertains to the nature of the adverse life events assessed. Different events may be more or less adverse, and the combination of adverse events into one variable may have led to a loss of information. For example, we treated having been fired or laid off from one's job as a vulnerability-inducing event; however, this may not be true for individuals who take advantage of unemployment benefits or are wealthy. Similarly, we did not count some stressful life events as being necessarily adverse, for example due to a lack of objectivity or specificity (see Methods section for omitted items). Second, we could not rule out that those with anxiety disorder onset are also likelier to report experiencing adversity, for example, on account of pessimistic interpretation biases (Mathews et al., 1997). Third, despite the large sample size of the NESARC, there were few cases of recurrent onset, leading to a relatively imprecise estimate. Relatedly, the high frequency of first onset of Specific Phobias is at odds with population data suggesting that the first incidence of phobias occurs most frequently early in life (Beesdo et al., 2010; Eaton et al., 2012). It might generally be the case that recall errors or biases for past episodes of anxiety led to the misclassification of many cases of recurrent onset as cases of first onset (Moffitt et al., 2010; Takayanagi et al., 2014). Those with anxiety disorders at Waves 1 and 2 were not counted as cases of recurrent onset as these were conceptualized as cases of persistence; this exclusion criteria may have also contributed to the large discrepancy between prevalence estimates of first and recurrent onsets.

Overall, these results support and extend the findings of previous studies in clinical samples (Finlay-Jones and Brown, 1981; Francis et al., 2012; Taher et al., 2015). Although our study did

not include some important events that were measured in other studies (Francis et al., 2012; Taher et al., 2015) because these were not captured by the AUDADIS, the overall result of our study is compatible with previous work. We would like to see the findings of the analyses on anxiety disorder sub-types and on the risk of first and recurrent onset replicated in independent samples. Finally, more extensive longitudinal studies with frequent follow-ups that can minimize recall biases for adverse events and episodes of anxiety would be better suited to understand the causal relationship between adverse life events and the onset of anxiety disorder.

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Table 1. Raw frequency and weighted prevalence of adverse events at Wave 1, and by anxiety disorder onset at Wave 2

Adverse Events	<i>Wave 1</i>			<i>Frequency (%) of Anxiety Disorder Onset at Wave 2 Conditional on Adverse Event</i>								
	frequency	%	se	<i>Panic Disorder</i> (n=964)	<i>Social Phobia</i> (n=825)	<i>Specific Phobia</i> (n=2,252)	<i>GAD</i> (n=1,321)	<i>Any Anxiety Disorder</i> (n=4,234)				
Death of family or friend	13,779	31	0.4	386 (40)	262 (32)	787 (35)	467 (35)	1,502 (35)				
Illness or injury of family or friend	14,981	36	0.5	423 (44)	327 (40)	909 (40)	605 (46)	1,751 (41)				
Victim of crime	2,765	7	0.2	100 (10)	88 (11)	178 (6)	146 (11)	398 (9)				
Financial crisis	5,037	11	0.3	237 (25)	181 (22)	379 (8)	325 (25)	827 (20)				
Fired or laid off	2,691	6	0.2	96 (10)	75 (10)	164 (7)	94 (7)	322 (8)				
Dissolution of relationship	2,790	5	0.1	109 (11)	88 (11)	187 (8)	139 (11)	402 (10)				
Any adverse event	24,716	57	0.6	689 (71)	530 (64)	1,443 (64)	916 (69)	2,811 (66)				

<i>Table 2. Odds Ratios (and 95% CIs) of Wave 1 variables as predictors of any past-year anxiety disorder at Wave 2</i>		
	Crude:	Adjusted ^a :
Age	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Sex		
Male	Reference	Reference
Female	1.95 (1.80-2.11)	1.84 (1.68-2.01)
Education		
Bachelor's degree	Reference	Reference
Some college	1.36 (1.22-1.50)	1.20 (1.08-1.34)
Completed high school or equivalent	1.24 (1.10-1.39)	1.23 (1.09-1.38)
Less than high school	1.37 (1.18-1.58)	1.43 (1.23-1.66)
Marital status		
Married or cohabiting	Reference	Reference
Widowed, divorced or separated	1.19 (1.07-1.33)	1.07 (0.95-1.20)
Never married	1.34 (1.16-1.45)	1.12 (0.93-1.17)
Urbanicity		
Urban	Reference	Reference
Rural	1.07 (0.95-1.21)	1.11 (0.98-1.26)
Lifetime Mood Disorders		
Negative	Reference	Reference
Positive	2.74 (2.47-3.03)	1.93 (1.72-2.16)
Lifetime Substance Use Disorder		
Negative	Reference	Reference
Positive	1.31 (1.19-1.44)	1.20 (1.08-1.33)
Lifetime Anxiety Disorders		
Negative	Reference	Reference
Positive	2.40 (2.20-2.62)	1.61 (1.47-1.77)
Any Past-Year Adverse Event		
Negative	Reference	Reference
Positive	1.51 (1.38-1.65)	1.23 (1.11-1.35)

^aAdjusted for age, sex, education, marital status, urbanicity, lifetime mood, anxiety and substance disorders

Table 3. Raw frequency and weighted proportion of first and recurrent onset of anxiety disorders at Wave 2

	<i>First Onset</i>			<i>Recurrent Onset</i>		
	frequency	%	se	frequency	%	se
Panic Disorder	814	2.3	0.1	150	0.2	0.02
Social Phobia	723	1.9	0.1	57	0.1	0.02
Specific Phobia	2,075	5.6	0.2	143	0.4	0.03
Generalized Anxiety Disorder	1,210	3.4	0.1	111	0.3	0.03
Any Anxiety Disorder	3,885	10.7	0.2	500	1.3	0.07

Table 4. Odds Ratios (and 95% Cis) of first and recurrent onset of anxiety disorders at Wave 2

	<i>First Onset</i>		<i>Recurrent Onset</i>	
	Crude:	Adjusted ^a :	Crude:	Adjusted ^a :
Age	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.99-1.00)	0.99 (0.98-1.00)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.89 (1.73-2.06)	1.86 (1.69-2.04)	2.53 (1.96-3.25)	2.26 (1.74-2.94)
Education				
Bachelor's degree or higher	Reference	Reference	Reference	Reference
Some college	1.39 (1.25-1.56)	1.25 (1.11-1.39)	1.15 (0.86-1.53)	1.02 (0.76-1.35)
Completed high school or equivalent	1.29 (1.14-1.46)	1.28 (1.13-1.45)	0.99 (0.73-1.34)	1.03 (0.75-1.40)
Less than high school	1.42 (1.22-1.65)	1.48 (1.26-1.72)	1.07 (0.76-1.51)	1.16 (0.82-1.65)
Urbanicity				
Urban	Reference	Reference	Reference	Reference
Rural	1.06 (0.93-1.20)	1.10 (0.96-1.25)	1.25 (0.94-1.64)	1.35 (1.00-1.81)
Marital Status				
Married or cohabiting	Reference	Reference	Reference	Reference
Widowed, divorced or separated	1.20 (1.07-1.35)	1.09 (0.96-1.23)	1.21 (0.92-1.60)	0.90 (0.67-1.20)
Never married	1.35 (1.20-1.52)	1.06 (0.95-1.20)	0.81 (0.61-1.08)	0.67 (0.49-0.93)
Lifetime Mood Disorders				
Negative	Reference	Reference	Reference	Reference
Positive	2.41 (2.16-2.69)	1.97 (1.76-2.22)	7.69 (6.11-9.67)	5.95 (4.69-7.56)
Lifetime Substance Use Disorders				
Negative	Reference	Reference	Reference	Reference
Positive	1.24 (1.12-1.38)	1.20 (1.08-1.34)	2.12 (1.69-2.65)	1.76 (1.40-2.22)
Any Past Year Adverse Life Event				
No	Reference	Reference	Reference	Reference
Yes	1.48 (1.35-1.63)	1.26 (1.14-1.39)	1.75 (1.38-2.23)	1.16 (0.91-1.47)

^aAdjusted for age, sex, education, marital status, urbanicity, lifetime mood, anxiety and substance disorders