

Life events and early onset depression: cause or consequence?

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ABSTRACT

Background. Adverse life events prior to episodes of depression are assumed to play a causal role. Earlier studies have, however, not adequately controlled for the potential confounding effects of previous depression.

Method. A two-phase study was nested within a six-wave population based cohort study of 1947 adolescents. Interviews at two assessment phases with the CIS-R and CIDI were used to generate ICD-10 diagnoses of depressive disorder. Life events with longer-term contextual threat were reported for the 6 months before first diagnosis and categorized on the basis of participant appraisal as negative and neutral/positive in effects. Previous depressive and anxiety symptoms were measured 6 months earlier.

Results. Pre-existing depressive and anxiety symptoms predicted later events, increasing three-fold the risks for both neutral/positive and negative events in females and increased seven-fold the risk of negative events in males. Life events in turn predicted the onset of depressive disorder independently of previous symptoms. Single negative events held an over five-fold elevated risk and multiple events an almost eight-fold higher risk. Personal threat and loss were associated with disorder in females but not males.

Conclusions. The findings are consistent with a causal role for life events in early episodes of depression. The association also reflects a reciprocal relationship in which earlier symptoms predict later events, perhaps as a result of an individual's attempts to change unfavourable social circumstances.

INTRODUCTION

Life events commonly precede depressive episodes in adults and have been strongly implicated in the causation of depressive disorder (Brown & Harris, 1978; Andrews, 1981; Kendler *et al.* 1993; Hazell & King, 1996). However, because most of this work has taken place in adults with recurrent depressive disorder, confounding by pre-existing depression remains a strong possibility. Pre-existing symptoms have been found more predictive of eventual depressive symptomatology than life events and largely account for the association between discrete

events and an index episode of depression (Andrews, 1981). Earlier episodes might affect the occurrence of and response to subsequent events (Brown *et al.* 1987). Consistent with this view teenage episodes predict responses to life events in women at high risk of depressive disorder (Bifulco *et al.* 1998). Mediators of response to life events potentially affected by earlier depression include altered patterns of social support (Brown & Harris, 1978; Brugha *et al.* 1990) and coping style (Lazarus & Folkman, 1984; Bifulco & Brown, 1996).

Ideally, study of a causal role for life events in depressive disorder would commence around the time of first onset. First episodes become common from the mid-teens, a time when female rates also diverge from male rates (Kessler *et al.*

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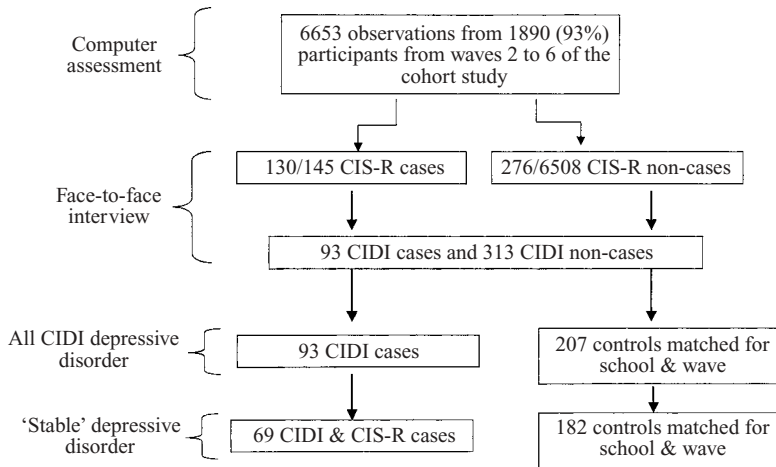


FIG. 1. Design of a nested case-control study of life events in adolescent depressive disorder.

1993). The available studies have consistently found high rates of life events prior to the onset of disorder but have been limited in addressing questions of causation (Wolchik *et al.* 1993; Goodyer, 2001). Most have taken place in clinical settings but because life events commonly trigger referral, there are problems in their interpretation (Paykel & Cooper, 1992; Sandberg *et al.* 2001). Population-based studies have avoided referral bias but have tended to focus on depressive symptoms rather than disorder (DuBois *et al.* 1992; Monck *et al.* 1994), on younger groups before the age of peak onset of disorder (Goodyer *et al.* 1993*a*), been limited to the study of females (Goodyer *et al.* 1993*a*; Monck *et al.* 1994) or used parental report of life events alone, appropriate in children, but less useful in older adolescents (Monck & Dobbs, 1985; McNeill *et al.* 1988). No study has so far incorporated prospective data on pre-existing depressive symptoms.

The present report derives from the Victorian Adolescent Health Cohort Study, a population-based prospective study commencing in the early teens. It addresses a question of the extent to which life events predict the onset of first episodes of depressive disorder independent of previous depressive and anxiety symptoms?

METHOD

Study sample (Fig. 1)

Between August 1992 and July 1995, we conducted a cohort study of adolescent health in the

state of Victoria, Australia. Two classes were selected at random from each of 44 schools drawn from a stratified frame of government, Catholic and independent schools in this state (total student numbers 60 905). School retention rates to year 9 in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) and the second class entered 6 months later, early in the tenth school year (wave 2). Participants were subsequently reviewed at a further four 6-monthly intervals, leading to a total of five or six waves depending on the entry point.

The current nested study took place between waves 2 and 6. Overall, 1947 (95.8%) of 2032 students on the class registers completed the first phase (cohort) questionnaire at least once during the study. The participant sex ratio (males 47.0%) was similar to that in Victorian schools at the time of sampling (Australian Bureau of Statistics, 1993). The mean age (s.d.) at wave 1 was 14.5 (0.5) and at wave 6, 17.4 (0.4) years.

Assessment procedure (Fig. 1)

The computerized revised Clinical Interview Schedule (CIS-R) was used to assess current depression in the main cohort study (Mann *et al.* 1983; Lewis & Pelosi, 1992). The CIS-R is a branched questionnaire, based on a structured psychiatric interview designed for use in community settings, with subscales providing data on the frequency, severity, persistence and intrusiveness of 14 common psychiatric symptoms.

All CIS-R cases of ICD-10 depressive episode was selected for a second phase face-to-face interview. A sample of CIS-R non-cases were also selected at random from participants in the same school and wave of data collection in a 2:1 ratio to cases. One hundred and forty-five participants fulfilled CIS-R criteria for depression between waves 2 and 6 of whom 130 (90%) completed the interview. Two hundred and ninety participants were selected from a total of 6508 CIS-R non-case observations, of whom 276 (95%) were interviewed. Reasons for non-participation were persistent absenteeism or interview non-attendance ($N=22$), parental refusal ($N=5$) and premature termination of interview ($N=5$).

Face-to-face interview assessment included a further diagnostic assessment and a measure of recent life events.

CIDI depression and hypomania modules

The depression and hypomania modules of the Composite International Diagnostic Interview (CIDI, Core Version 1.1) were used to generate life time ICD-10 diagnoses for affective disorder (Robins *et al.* 1988; WHO, 1993). The CIDI is a structured diagnostic interview devised for use by non-medical professionals after a standardized training (Robins *et al.* 1988). A research psychologist, trained in the use of the CIDI and blind to first-phase status, conducted these interviews at a subject's school within 3 weeks of completion of at least 70% of first phase assessments in that school. CIDI cases were excluded from selection for phase 2 at subsequent study waves. Two groups with depressive disorder were defined: all those diagnosed by the CIDI; and a second group with 'stable' depressive disorder who fulfilled criteria for depressive disorder on both the CIS-R and the CIDI.

Recent life events

Recent life events were measured using an adaptation of the List of Threatening Experiences Questionnaire, a brief inventory for use in population-based studies of events with considerable long-term contextual threat (Brugha *et al.* 1985; Brugha & Cragg, 1990). Equivalent items were modified in their focus to be appropriate for an adolescent group (e.g. 'split-up with boyfriend/girlfriend' rather than 'marital separation or divorce') and administered as a

self-report questionnaire prior to the CIDI assessment. Subjects reported the occurrence of each event in the previous 6 months and rated its desirability at the time of occurrence as positive, neutral or negative. Positive and neutral events were categorized together and distinguished from negative events.

Events were subclassified into network and personal categories: network events involved either the immediate family (illness, injury or death of a close relative, death of an immediate family member, parental separation or divorce) and broader social network (death of a close friend or other relative, split up with boyfriend/girlfriend, serious conflict with a friend, neighbour or relative); personal events involved either personal loss or threat (serious personal illness, injury or assault, financial crisis involving self or immediate family, having something valuable lost or stolen) or setbacks (failing an important exam or falling behind in school-work, suspension from school or leaving school as not going well, police arrest or court appearance).

Earlier depressive and anxiety symptoms

Earlier depressive and anxiety symptoms were assessed using the CIS-R total score at the previous wave of cohort data collection including wave 1. A cut-off point of ≥ 12 defined those with a high level of pre-existing anxiety or depressive symptoms (Lewis *et al.* 1988; Lewis & Pelosi, 1992).

Analysis

We analysed the data with Stata software (StataCorp, 2001). Associations of depressive disorder with variables of interest were examined using conditional logistic regression with matching defined by school and wave of selection. Inverse probability weighting was used to estimate the cumulative prevalence of depressive disorder and rates of life events in the previous 6 months (Pickles *et al.* 1995). For CIS-R (first phase) cases, weights were the inverse of the participation rates at the parental interview phase. For CIS-R (first phase) non-cases (controls), probabilities of phase 2 participation were estimated for each school across all study waves combined. The 44 schools were then grouped into thirds corresponding to high, intermediate and low probabilities of control participation. Within each group a subject's

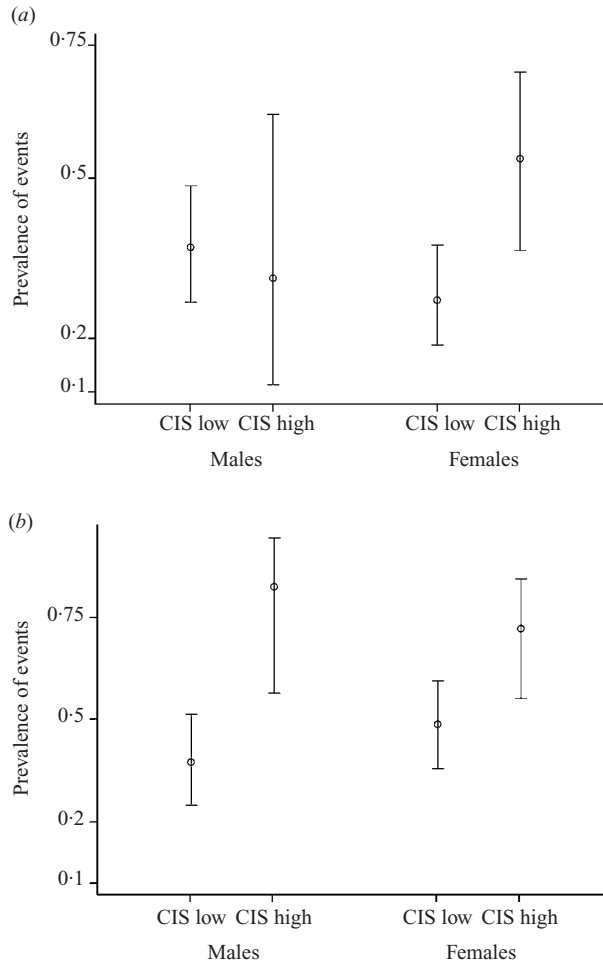


FIG. 2. Report of (a) any neutral/positive and (b) negative events in 15–17 year-old adolescents classified by sex and level of depressive and anxiety symptoms 6 months earlier.

weight was the ratio of the number of participants to the total number of observations. These prevalence estimates are accompanied by 95% confidence intervals estimated using Stata's svy procedures.

RESULTS

CIS-R data were available from a measurement point 6 months earlier in 367 (96%) of the 382 second phase participants. The association of previous high depression and anxiety with subsequent life events is illustrated in Fig. 2(a) and (b). In girls, the occurrence of any negative event (OR 2.8, 1.2, 6.6) and any neutral/positive event

(OR 3.1, 1.3, 7.3) was higher in the group with previous high CIS-R scores. In boys, the rate of negative events (OR 7.3, 1.9, 28) was higher in the group with previous morbidity.

Depressive disorder and life events

Matched pairs or triplets for CIDI defined depressive disorder (i.e. at least one case and one control from a specific school and wave of selection) were available for 93 cases and 207 controls. For stable depressive disorder 69 cases were matched with 182 controls.

Table 1 shows rates of life events in participants for both CIDI defined and stable depressive disorder. Reports of negative life events were

Table 1. Association of recent life events, classified by event type and appraisal, with ICD-10 depressive disorder in 300 adolescent participants in the case-control study*

	Neutral/Positive rating				Negative rating			
	Disorder (N=93) %	No disorder (N=207) %	OR (CI)	Adjusted† OR (CI)	Disorder (N=93) %	No disorder (N=207) %	OR (CI)	Adjusted† OR (CI)
Network events								
Family	10	11	0.8 (0.3-1.9)	0.8 (0.3-2.2)	39	18	3.1 (1.6-5.7)	2.4 (1.2-5.0)
Extended network	9	16	0.4 (0.2-0.9)	0.6 (0.2-1.5)	65	34	3.3 (1.8-5.9)	2.5(1.3-4.9)
Personal events								
Personal loss/threat	5	10	0.4 (0.1-1.3)	0.3 (0.1-1.0)	43	18		M 0.5 (0.1-3.2) F 3.3 (1.1-4.9)
Setbacks	11	12	1.0 (0.4-2.3)	0.8 (0.3-2.3)	47	24	2.7 (1.4-5.1)	1.8 (0.9-3.6)
All events								
Any category	23	33	0.7 (0.4-1.2)	0.7 (0.3-1.4)	89	54	6.6 (2.9-15)	4.0 (1.6-10)
Multiple categories	21	11	0.3 (0.1-1.0)	0.3 (0.1-1.3)	60	28	3.7 (2.1-6.7)	2.8 (1.4-5.6)

* Figures are weighted percentages and odds ratios with 95% confidence intervals in brackets.

† Adjusted for previous morbidity.

Boldtype indicates odds ratios statistically significant at P ≤ 0.05.

Table 2. Association between depressive disorder and recent life events, classified by desirability and events numbers, with adjustment for depressive and anxiety symptoms 6 months earlier

	All CIDI cases and matched controls (N = 300)		Stable depression (CIDI and CIS-R) and matched controls (N = 251)	
	Univariate OR	Adjusted OR*	Univariate OR	Adjusted OR*
Positive events				
Single	0.8 (0.4-1.6)	0.9 (0.4-2.0)	0.7 (0.3-1.5)	0.65 (0.2-1.8)
Multiple	0.25 (0.08-0.8)	0.5 (0.1-1.9)	0.2 (0.05-0.8)	0.1 (0.01-1.4)
Negative events				
Single	4.5 (1.8-11)	2.7 (0.9-7.6)	8.4 (2.5-28)	5.2 (1.3-22)
Multiple	9.1 (3.8-22)	4.9 (1.8-13)	14 (4.4-46)	7.9 (2.0-30)
Previous depressive & anxiety symptoms	6.7 (3.5-13)	4.9 (2.4-10)	8.4 (3.8-19)	8.0 (3.2-20)

* Figures are odds ratios (95% confidence intervals) from multivariate logistic regression models with all variables fitted concurrently and with adjustment for sex, parental separation and age.

Boldtype indicates odds ratios statistically significant at P ≤ 0.05.

common with over half of the control subjects reporting at least one event in the previous 6 months. Events rated as a neutral or positive were reported by a third of the control group. Substantial associations were found with each category of negative life event. An interaction (P = 0.06) was found between sex and events involving personal loss/threat in that these events were associated with an over three-fold increase in risk in girls but not boys.

Life events and subsequent depressive disorder (Table 2)

The association between life events and depressive disorder was considered in two further

models with adjustment for previous depressive and anxiety symptoms. In the first model all CIDI cases were compared with matched controls. After adjustment for previous morbidity the associations with both negative and neutral/positive life events were substantially reduced. Only multiple negative life events retained a clearly significant association with depressive disorder.

The second model examined the association of life events with stable (i.e. CIS-R and CIDI) depressive disorder. Single negative events were associated with a five-fold increase in the odds for depressive disorder and multiple events with an almost eight-fold increase. Although a trend

for a protective association with neutral/positive events remained the confidence intervals were too broad to ascribe significance.

DISCUSSION

Life events are common in adolescents. Around a half of the control group reported one or more negative events in the previous 6 months. The great majority who experienced negative events did not develop depressive disorder.

Life events did predict the onset of depressive disorder independently of previous symptoms. Single negative events predicted a three to five-fold higher rate and multiple events a five to eight-fold higher rate of disorder. Event appraisal emerged as a clear mediator, in that events construed as positive or neutral tended to diminish risks for subsequent disorder whereas negatively appraised events increased risk. However, the relationship between recent life events and early onset depression appears more complex than a simple proposition that life events cause depressive disorder. Earlier depressive and anxiety symptoms predicted both subsequent life events and depressive disorder. For females the experience of both negative and neutral-positive events was around three-fold higher in those with earlier depressive and anxiety symptoms. For males negative events were seven-fold higher in this group.

Earlier studies of life events and adolescent depression have differed in subject age, type of informant, life event assessment instrument and period of assessment. Even so, this studies findings of very high rates antecedent adverse events in cases and their relatively common occurrence in comparison subjects are consistent with this earlier work (Garrison *et al.* 1987, 1992; Goodyer, 1990; Adams & Adams, 1991; Goodyer *et al.* 1993*b*; Williamson *et al.* 1998).

This study's strengths derive from its population-based sample, high response and retention rates and prospective data on pre-existing symptoms. The cohort extended over the period of peak incidence of first episodes. Its serial screening strategy over a period of 2½ years was designed to identify newly emerging disorder and the majority of cases reported no earlier episodes. It is therefore well placed to focus on the role of life events in the initiation of disorder.

Some limitations should be noted. Very early school leavers tend to have high levels of psychiatric morbidity and adversity and were not included (Thompson *et al.* 1994). Selectional biases may also have arisen in that males and subjects with divorced parents, both factors related to depressive disorder, had lower phase 1 response rates. An overall participation rate of 96% did much to ensure participation at some point but it is possible that these characteristics were under-represented in the interview phase. Lastly, life events were measured retrospectively using the List of Threatening Experiences Questionnaire (LTE). It was designed to measure events in larger scale studies where resources do not allow extensive interviews. Its adaptation is supported by evidence that adolescents rate the severity of individual life events in a similar way to adults and are well able to rate the impact of events on the self (Goodyer, 1990, 1996). Even though the participants were asked rate events in the past 6 months, with the previous assessment as a reference point, it is not possible to exclude some error in the reported timing of events.

Differences in the experience of social adversity have previously been suggested as explanations for the sex difference in adult depression (Kessler & McLeod, 1984; Nazroo *et al.* 1997). A different appraisal of events in adolescent females has previously been noted in some previous adolescents (Burke & Weir, 1978; Petersen *et al.* 1991; Compas, 2000). In this study the similarities between males and females in both the report and appraisal of life events were more striking than the differences. However, girls responded differently to events involving personal threat or loss (assault, illness, injury and financial problems). This finding is consistent with a recent report that social victimization is associated with depressive symptoms in teenage girls but not boys (Bond *et al.* 2001). This sex difference in response to events such as assault, injury and illness may contribute to a higher rate of depressive disorder in adolescent girls.

The association between life events and adolescent depressive disorder can neither be fully explained by earlier depression nor is it the result of a simple causal relationship (Andrews, 1981). Rather the association appears reciprocal with recent events altering risks for depression,

and depressive symptoms in turn altering risks for future life events. Social, psychological and biological processes might all underlie this pattern of association. Longer standing social difficulties may increase the risk for major events at the same time as causing emotional distress. Thus, a link between earlier depressive and anxiety symptoms and life events may reflect confounding by longer standing social adversity. Confounding with individual personality and coping styles is a further possibility. Depressive symptoms and higher levels of life events might both arise from a pre-existing temperament or interpersonal style that in turn predicts major depression (Guthrie *et al.* 1991; Ward *et al.* 2000).

A further possibility is that an experience of depressive and anxiety symptoms promotes attempts by an individual to change a social context, perceived as undesirable (Henderson, 1974). The finding that earlier depressive and anxiety symptoms predict positive as well as negative events is perhaps most consistent with this view. Where the outcome is favourable, risks for progression to depressive disorder diminish but, in generating negative events, risks increase. There also is some support for this hypothesis in the type of life events predicted. Personal events (e.g. injury, assault, financial problems, failing exams) and those involving the extended network (interpersonal conflict, relationship ending) were the event categories most clearly associated with earlier depressive and anxiety symptoms. Although not formally rated for independence, these event categories are less likely to be independent and more likely to arise as a result of an adolescent's own actions.

Such a pattern of onset suggests that preventive and early interventions aiming to shift the social context and profile of subsequent events in adolescents with subsyndromal levels of depression may be warranted. Promoting positive rather than negative social changes for these individuals may avert a progression to depressive disorder. For girls, reducing the prevalence or impact of personal threats, assaults and injuries might be a particular focus in reducing rates of depression.

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