Article

The Interplay and Etiological Continuity of Neuroticism, Difficulties, and Life Events in the Etiology of Major and Subsyndromal, First and Recurrent Depressive Episodes in Later Life

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Objective: Stressful life events, long-term difficulties, and high neuroticism are established risk factors for depression. Less is known about their role in late-life depression, how they modify or mediate one another's effects, and whether this differs between major and subsyndromal, first and recurrent episodes.

Method: The authors used a prospective case-control design nested in a community survey of elderly subjects that included a measure of neuroticism. They compared 83 survey participants who subsequently developed a depressive episode with 83 randomly selected comparison participants. The authors determined dates of onset, history, and severity of episodes and dates of occurrence and severity of stressful life events and difficulties.

Results: Stressful life events did not mediate the effects of high neuroticism and difficulties at onset, possibly because of the uncontrollable nature of common stressful life events in later life. Without both high neuroticism and difficulties, stressful life events did not increase risk. High neuroticism and difficulties increased risk, even without a stressful life event. In the presence of high neuroticism and/or difficulties, the depressogenic effect of stressful life events was substantial, suggesting effect modification. The authors found no evidence to suggest etiological discontinuity between major and subsyndromal episodes. First and recurrent episodes showed a discontinuous pattern of associations. Severe stressful life events had weaker associations, but high neuroticism and mild stressful life events had stronger associations with recurrent than with first episodes.

Conclusions: This study demonstrated the usefulness of a dynamic stress-vulnerability model for understanding late-life depression. Evidence was found suggesting etiological discontinuity between first and recurrent but not between major and subsyndromal episodes.

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The significance of stressful life events in the etiology of depression is well established. In addition, substantial evidence implicates long-term difficulties (1–4) and the personality trait of neuroticism (3, 5, 6), which is equivalent, or closely related, to "harm avoidance" (7), "autonomic lability" (8), and "stress reactivity" (9). Neuroticism has been interpreted as a marker of "psychobiological vulnerability" (3, 6, 10), and long-term difficulties, such as a chronically ill spouse and poverty as a marker of "environmental vulnerability." According to the dynamic stress-vulnerability model (2, 11), vulnerability factors may influence risks of onset of depressive episodes by the generation of stressful life events (mediation) and amplification of their effects (modification). Studies in nonelderly samples generally support these assumptions (2–6, 10, 12–14).

Less is known about how neuroticism level, long-term difficulties, and stressful life events affect the risks for late-life episodes of depression. Also unclear is whether major and subsyndromal depressive episodes and first and recurrent episodes represent underlying etiological continua or whether they are distinct syndromes with qualitatively different etiologies. Etiological continuity implies similarity of risk factors for major and subsyndromal and for first and recurrent episodes.

Using a prospective case-control design nested in a community survey of noninstitutionalized elderly individuals, we examined whether neuroticism level, long-term difficulties, and stressful life events modify and/or mediate one another's effects and whether their associations with onset differ between major and subsyndromal and between first and recurrent episodes. Guided by the dynamic stress-vulnerability model (2, 11, 13) and previous work in younger age samples (2–6, 10, 12–14), we proposed the following hypotheses regarding effect mediation and modification:

1. High neuroticism level and long-term difficulties are associated with onset partly because they increase exposure to stressful life events; i.e., stressful life events medi-

ate some of the risks associated with neuroticism and long-term difficulties.

2. High neuroticism level and long-term difficulties modify the effect of stressful life events; i.e., the risk of stressful life events is amplified in the presence of long-term difficulties and neuroticism.

With regard to subsyndromal versus major episodes, we hypothesized

3. Similar associations of stressful life events, long-term difficulties, and high level of neuroticism with onset of subsyndromal as well as major depressive episodes, and thus etiological continuity (15–18).

With regard to first versus recurrent episodes, we expected—assuming that a personal history of depression indicates higher vulnerability—

4. Differential associations of onset with selected risk factors (19, 20), and thus etiological discontinuity. Mild stressful life events are associated with onset of recurrent but not first episodes, whereas severe stressful life events are more strongly associated with first than recurrent episodes because mild stressful life events have already removed the most vulnerable from the population at risk, i.e., those with a history of depression.

Method

We used a prospective case-control design nested in a community survey of 3,700 noninstitutionalized elderly individuals.

Selection of Subjects

In this nested case-control design, depressed and comparison subjects were recruited during a 24-month period ending April 1998 from the 3,700 then-available participants of a community survey on quality of life that was carried out in 1993 among persons aged 57 years or more (for details, see reference 21). The depressed subjects were persons who had experienced a subsyndromal or major depressive episode (definition to follow) that had started in the 9 months preceding the clinical interview.

The depressed subjects were selected in three stages. The first stage involved two complementary approaches: examining the records of general practitioners and conducting a screening questionnaire. During the 24-month recruitment period, a research physician checked the medical records of all survey participants monthly and identified 83 whom the general practitioner had diagnosed as having depressive illness. In addition, because older people often do not appear depressed or are not diagnosed as such by general practitioners, we also screened twice for a recent onset of depression using the Geriatric Depression Scale (22) with a 1-month time frame. In total, 7,566 Geriatric Depression Scale questionnaires were sent out, of which 85.4% were returned fully completed. The 269 persons with a Geriatric Depression Scale score of six or more and a probable depression core symptom were considered to be study participants.

Using a brief telephone interview (the second stage), of the 347 individuals who were diagnosed as having depression, we identified 202 persons who had at least one depression core symptom that had emerged in the previous 9 months (84 had no recent symptoms; 61 refused to answer). The third stage comprised the clinical interview. Of the 202 eligible persons, 19 (9.4%) were excluded because of incomplete or unreliable data, 18 (8.9%) did not meet the diagnostic criteria for (subsyndromal) depression, 49 (24.3%) did not meet the criterion for recent onset (i.e., within 9 months), 14 (6.9%) refused to participate in the clinical interview, and 19 (9.4%) were unprepared or unable to complete the life stress interview, leaving 83 subjects with complete data.

Comparison subjects were selected at random from the available 3,700 survey participants. Hence, the comparison subjects were not necessarily free of depressive symptoms. Of 102 possible comparison subjects approached, 83 (81.4%) agreed to participate.

Instruments and Measures

Depression. Diagnostic assessment was with the 10th version of the Present State Examination (PSE) module from the Schedules for Clinical Assessment in Neuropsychiatry (23). Respondents were asked to indicate the 4-week period during the last 3 months preceding the interview at which they felt worst; that period was assessed by means of the PSE. The comparison subjects were not interviewed with the PSE. We distinguished two categories of depressive episode: major episode if the criteria for a DSM-IV major depressive episode were met (N=25, 30.1% of depressed subjects) and subsyndromal episode (N=58, 69.9%). The latter category was defined as having at least three symptoms (including depressed mood or loss of interest or pleasure) of subclinical severity or two symptoms of clinical severity and no major depression. "Subclinical severity" means that the symptom was present but to a degree insufficient for diagnostic classification according to the PSE/DSM-IV criteria. Depressive symptoms were not scored if they were attributable to direct physical effects of substance use or somatic illness or to bereavement.

After administration of the PSE, information on the history of depression was gathered with an interview especially developed for this purpose. "First episode" means that there (probably) had never been a previous subsyndromal depressive episode. "Recurrent episode" means that there had been at least one previous episode that would have met the criteria for at least a subsyndromal depressive episode. "Onset" refers to the transition from not meeting research criteria for at least a subsyndromal episode to meeting the criteria for a subsyndromal or major depressive episode. Since it is difficult to date onset, particularly if insidious, a calendar including neutral markers like national and local events, holidays, and birthdays of close relatives was used to anchor date of onset. We determined the week of transition by extensive probing, including eliciting information from significant others.

Stressful life events and long-term difficulties. We used Brown and Harris's Life Events and Difficulties Schedule (2, 24) to elicit and rate stressful life events and long-term difficulties in the 12 months preceding the interview. The Life Events and Difficulties Schedule is an investigator-based, semistructured interview with excellent measurement properties yielding contextual ratings on a number of characteristics of events and difficulties, such as severity, type, and relatedness to psychiatric illness.

Because earlier work had shown that the rate of stressful life events began to diverge between depressed and comparison subjects 3–4 months before onset (25), only stressful life events occurring in the 3 months preceding the onset of the index episode were used for the present analyses. On average, onset occurred 4.7 months before the Life Events and Difficulties Schedule interview with the depressed subjects; in other words, the mean Life Events and Difficulties Schedule reference period for depressed subjects was between 7.7 and 4.7 months before the interview. Therefore, this period was also chosen as the reference period for comparison subjects.

For "stressful life event," we defined occurrences with a rating of 1–4 on the Life Events and Difficulties Schedule's 4-point contextual long-term threat scale (1=mild, 2=moderately severe, 3=severe, 4=very severe) that were (probably) not due to insidious depressive symptoms. We examined three variables for dichotomous stressful life event: 1) at least one event of at least mild (rat-

TABLE 1. Relation of Baseline Neuroticism, Long-Term Difficulties, and Stressful Life Events to Onset of Subsyndromal or Major Depression Over 9 Months in Elderly Community Subjects

	Comparison Subjects (N=83)		Subjects Who Became Depressed (N=83)			
Measure	N	%	N	%	Odds Ratio	90% CI
High baseline level of neuroticism[a]	24	29.3	53	63.9	4.27	2.47–7.39
Long-term difficulty[b]						
At least moderately severe	34	41.0	56	67.5	2.99	1.76–5.09
Severe	11	13.3	25	30.1	2.82	1.46–5.47
Stressful life events[b]						
Any	21	25.3	44	53.0	3.33	1.92–5.78
At least moderately severe	15	18.1	36	43.4	3.47	1.92–6.29
Severe	1	1.2	18	21.7	22.71	4.10–125.78

[a] Defined as a score of 5 or higher on the Dutch version of the Brief Revised Eysenck Personality Questionnaire (26). Data available for 82 comparison subjects.
[b] Measured with the Life Events and Difficulties Schedule (2, 24).

ing≥1) severity, 2) at least one event of at least moderate (rating≥2) severity, and 3) at least one severe or very severe (rating≥3) event.

For long-term difficulty, we defined persistent life stress with a rating of 1–6 on Brown and Harris's contextual threat rating scale that was present during the reference period (probably), not due to insidious depressive symptoms, and dated from before the reference period. We examined two variables for dichotomous long-term difficulty: 1) at least one difficulty of at least moderate severity (rating≥3) and 2) at least one severe or very severe difficulty (rating≥4).

Neuroticism. Neuroticism level was measured during the 1993 survey with the Dutch version of the Brief Revised Eysenck Personality Questionnaire (26). The neuroticism scale consisted of 12 binary (yes/no) items and had an internal consistency (Cronbach's alpha) of 0.82. The scale was dichotomized at a cutoff score of 5 (0–4 versus ≥5).

Statistical Analysis

The data were analyzed by means of logistic regression analyses, with depression onset (depressed versus comparison subjects) as the outcome variable. Odds ratios were used to express the strength of association between predictors and onset of depression. Because we had clear directional hypotheses, a one-tailed p value <0.05 was considered statistically significant.

To examine the hypothesis that stressful life events mediate part of the association of high neuroticism level and long-term difficulties with later onset, we estimated adjusted odds ratios in multivariate analyses. If the adjusted odds ratios are considerably smaller than the unadjusted odds ratios, mediation is possible.

The hypothesis that high neuroticism level and long-term difficulties enhance the risk of depression associated with stressful life events could not be answered in a straightforward manner (i.e., by testing the interaction terms) because the logistic regression model is multiplicative. The predictor variables are additively associated with the logit of the probability of onset but multiplicatively linked to the probability itself. Our hypothesis assumed additive interaction and is supported if the combined effect of stressful life events and high neuroticism level or long-term difficulties is stronger than the sum of the separate effects. Only additive interaction can be conceptualized biologically in an unambiguous way (27). We estimated additive interaction effects by comparing the odds ratios for the combined categories of two predictors (e.g., high neuroticism level and a severe stressful life event) with what would be expected in case of no interaction. In that event (i.e., independence of effects), odds ratio(AB) ≈ odds ratio(A) + (odds ratio)B – 1, assuming that the odds ratios are approximately equal to the relative risks (which is true for disorders with a reasonably low prevalence) and that they are larger than 1. (For more details, see, e.g., reference 27.)

Finally, to examine the hypotheses regarding an etiologic continuum, we performed multinomial logistic regression analyses, which allow for more than two outcome categories and can be used to test differences between subgroups.

Results

Descriptives and Univariate Associations

Table 1 shows the distribution of predictors in depressed (58 women, 69.9%; mean age=71.4 years, range=60–92) and comparison (46 women, 55.4%; mean age=71.9 years, range=62–91) subjects. The differences were as predicted, with more risk factors in depressed than comparison subjects. Even among depressed subjects, severe stressful life events (N=18, 21.7%) and severe long-term difficulties (N=25, 30.1%) were not common. Univariate logistic regression analyses confirmed the descriptive impressions. High baseline level of neuroticism, stressful life events, and long-term difficulties increased the risk of onset substantially. Adjusting for gender and age yielded virtually the same results.

Mediation

We did not find any support for the hypothesis that stressful life events mediate part of the association of high neuroticism level and long-term difficulties with episode onset. Adjusting for any of the stressful life event measures did not mitigate the association of neuroticism and long-term difficulties with depression onset.

Modification

Table 2 reports the combined effects of high neuroticism level, long-term difficulties, and stressful life events. We present two variants: one with any stressful life event and one with at least a moderately severe stressful life event. Since the two long-term difficulty measures yielded similar results, Table 2 presents only the results obtained with long-term difficulties of at least moderate severity.

The reference category was the group of persons with low neuroticism level who experienced neither a moderately severe long-term difficulty nor any stressful life event. The data in Table 2 show the following:

TABLE 2. Combined Effects of Baseline Neuroticism, Long-Term Difficulties, and Stressful Life Events on the Onset of Subsyndromal or Major Depression Over 9 Months in Elderly Community Subjects[a]

				Definition of Stressful Life Events							
				Any Stressful Life Event				At Least Moderately Severe Stressful Life Event			
	Status of Risk Factor			Percent of Subjects				Percent of Subjects			
Combination	Neuroticism Level[b]	Long-Term Difficulties of at Least Moderate Severity[c]	Stressful Life Events[c]	Comparison Subjects	Subjects Who Became Depressed	Odds Ratio	90% CI	Comparison Subjects	Subjects Who Became Depressed	Odds Ratio	90% CI
1	Low	No	No	32.9	7.2			37.8	7.2		
2	Low	Yes	No	19.5	7.2	1.69	0.57–4.98	20.7	10.8	2.74	1.01–7.43
3	High	No	No	9.8	12.1	5.62	1.92–16.51	9.8	13.3	7.10	2.46–20.49
4	High	Yes	No	12.2	20.5	7.65	2.84–20.60	13.4	25.3	9.86	3.79–25.65
5	Low	No	Yes	13.4	2.4	0.82	0.19–3.55	8.5	2.4	1.48	0.33–6.68
6	Low	Yes	Yes	4.9	19.3	18.00	5.52–58.68	3.7	15.7	22.39	6.20–80.83
7	High	No	Yes	2.4	10.8	20.25	4.59–89.31	2.4	9.6	20.67	4.64–91.98
8	High	Yes	Yes	4.9	20.5	19.13	5.89–62.09	3.7	15.7	22.39	6.20–80.83

[a] N=83 for both comparison and depressed subjects.
[b] Measured with the Dutch version of the Brief Revised Eysenck Personality Questionnaire (26). Low and high levels were defined as scores of 0–4 and ≥5 respectively.
[c] Measured with the Life Events and Difficulties Schedule (2, 24).

1. That any stressful life event has a strong impact on risk of onset in people with high neuroticism level and/or a moderately severe long-term difficulty.

2. But that any stressful life event does not affect risk of onset in individuals with neither a moderately severe long-term difficulty nor a high level of neuroticism. The same holds for at least moderately severe stressful life events. Stressful life events trigger episodes only in the presence of a high level of neuroticism and/or a long-term difficulty.

3. It does not matter whether the stressful life event occurs in combination with only a long-term difficulty, only a high level of neuroticism, or both. All corresponding odds ratios are between 18 and 23. Apparently, the combination of the two vulnerabilities does not add extra risk. Severe stressful life events seem to be linked with onset in the absence of neuroticism and long-term difficulties (odds ratio=5.29; 90% confidence interval [CI]=0.47–59.62). (Severe events did not occur in comparison subjects with a high level of neuroticism and/or a long-term difficulty; hence, the odds ratios in these subgroups could not be estimated. Therefore, data for severe stressful life events are not presented in Table 2.)

4. Both high neuroticism level and long-term difficulties are each associated with onset, even in the absence of a moderately severe stressful life event.

To examine potential two-way additive interactions further, we estimated the combined effect of a high level of neuroticism and stressful life events (odds ratio=15.53; 90% CI=6.20–38.90) and compared this with the odds ratio expected on the basis of only additive main effects, thus assuming no additive interaction (expected odds ratio=8.68). We did the same for the combination of long-term difficulties and stressful life events (odds ratio=9.28; 90% CI=4.11–20.97; expected odds ratio=2.89). Both combined effects are considerably stronger than expected on the basis of no additive interaction, although only one of the two expected odds ratios is smaller than the lower limit of the CI of the odds ratio for the combined effect. Both high level of neuroticism and a moderately severe long-term difficulty tend to amplify the effect of any stressful life event. Analyses with at least moderately severe stressful life events (thus disregarding mild stressful life events) yielded similar results.

Subsyndromal Versus Major and First Versus Recurrent Episodes

Using multinomial logistic regression analysis, we examined differences in the univariate effects between subsyndromal (69.9% of depressed subjects) and major (30.1% of depressed subjects) depressive episodes and between first (N=41, 49.4% of depressed subjects) and recurrent (N=42, 50.6%) episodes.

We did not find any evidence favoring qualitative differences in etiology between subsyndromal and major depressive episodes. The univariate effects, in terms of odds ratios, of high level of neuroticism (3.95 versus 5.14, respectively), moderately severe long-term difficulties (2.71 versus 3.08), any stressful life event (3.39 versus 3.20), moderately severe stressful life event (3.68 versus 3.02), and severe stressful life event (21.39 versus 25.89) were all significantly larger than 1, but none differed between subsyndromal and major episodes.

History of depression did make a difference. When comparing recurrent with first episodes, the effect of high level of neuroticism was significantly stronger for recurrent episodes (odds ratios=7.25 versus 2.30, respectively; χ^2=5.60, df=1, p=0.02), but the effect of severe stressful life events was weaker for recurrent episodes (odds ratios=9.11 versus 41.00; χ^2=5.75, df=1, p=0.02). Mild stressful life events (severity level 1 or 2) were associated with a higher risk of recurrence only in the subgroup of depressed subjects with recurrent episodes (odds ratio=2.94, 90% CI=1.48–

5.84, p=0.01, versus odds ratio=1.09, 90% CI=0.47–2.51, p=0.89) (difference: χ^2=3.29, df=1, p<0.07).

Discussion

This prospective, population-based, case-control study examined the interplay of stressful life events, long-term difficulties, and level of neuroticism in the etiology of subsyndromal and major, and first and recurrent episodes of depressive illness in later life. The results were generally unequivocal but should be interpreted cautiously given the following limitations.

Limitations

Various factors may have introduced selection bias, most notably the unavailability of some baseline participants for screening and the nonresponse of some who screened positive for depression and were eligible for further interviewing. We compared these groups with responders in terms of baseline characteristics (25). The general picture was that those who were not available were older and sicker, in particular, physically and cognitively. Although this selection bias has resulted in an undersampling of the very sick, there is no obvious reason to assume that this would have biased our estimation of the effects of risk factors, since major episodes did not differ etiologically from subsyndromal episodes. No significant differences were found between those who received the personal interviews (the PSE and the Life Events and Difficulties Schedule) and those who did not, except for age (nonresponders were 3 years older).

A second limitation is the possibility of information bias in that the same interviewer completed both the PSE and the Life Events and Difficulties Schedule. Although administration of the PSE preceded the Life Events and Difficulties Schedule usually by 1–2 weeks and interviewers were extensively trained in careful dating of symptom onset and the occurrence of stressful life events, we cannot ignore the fact that scoring on the Life Events and Difficulties Schedule was influenced by knowledge about depressive symptoms. However, because only events and difficulties were included in the analysis that had occurred in the 3 months preceding onset and these were rated as not being caused by insidious psychopathology, it is unlikely that the results suffered.

Another limitation is the small group size and, in particular, the few depressed subjects with episodes of major depressive disorder. This explains the extremely wide confidence intervals for odds ratios in some of the stratified analyses. Finally, we did not establish which subsyndromal episodes met the criteria for DSM-IV adjustment disorder. Our subsyndromal episodes reflect the diagnostic criteria as specified in the Method section and should not be confused with DSM-IV minor depressive disorder, although two-thirds of the subsyndromal episodes met the "A" criteria (number, duration, and severity of symptoms) for DSM-IV minor depressive disorder.

Implications

We did not find support for our hypothesis that stressful life events mediated the effects of high level of neuroticism and long-term difficulties on risk of depression onset. Neuroticism and long-term difficulties were not associated with the occurrence of stressful life events. This is inconsistent with the dynamic stress-vulnerability model (11), which assumes that vulnerability factors act, in part, by means of stress generation (3, 10, 12, 28). The inconsistency is perhaps due to the nature of common stressful life events in later life. Typical events in our study group involved loss of physical and mental capacities and of relationships and social contacts because of illness and aging. Consequently, older people may be predominantly exposed to stressful life events that are largely outside their control and thus independent of high level of neuroticism and long-term difficulties.

Consistent with the model, high level of neuroticism and long-term difficulties amplified the effect of stressful life events. This expands earlier findings for neuroticism and similar measures in younger samples (13, 14) to the population of older people. The amplification of the effect of a stressful life event by a long-term difficulty has not been demonstrated before, although it comes close to the observation of Brown and Harris (2) that a severe event that matches an existing difficulty confers a threefold higher risk in women than a severe event without a matching difficulty. What turns a long-term difficulty into an "active" risk (the timing of onset) seems to be the occurrence of a mild stressful life event whose effect is amplified by the preexisting long-term difficulty. Apart from amplifying the effects of stressful life events, high level of neuroticism and long-term difficulties were also associated with onset in those who did not experience a moderately severe stressful life event. This suggests the existence of other external or internal events that determine the timing of onset in vulnerable persons in the absence of a stressful life event.

Our results were consistent with the hypothesis of etiological continuity between major depression and subsyndromal states, at least as far as neuroticism and long-term adversity are concerned. This supports a dimensional view of severity and quantitative, not qualitative, etiologic differences. Although the diagnostic convention for major depressive episodes may be relevant for treatment, from an etiologic point of view, its value is unclear.

We found interesting differences in etiology between first and recurrent episodes, suggesting etiological discontinuity. The differences fit the notion of a higher vulnerability in those with recurrent episodes and, consequently, a sensitivity to even mild stressful life events. We do not know whether the current level of vulnerability of people with a previous history of depression reflects scarring (kin-

dling or sensitization) by earlier episodes (29) or whether it was already present before the first lifetime episode. Although consistent with findings of Frank et al. and Brown et al. (19, 20), the notion of higher vulnerability in people with recurrent episodes seems at odds with the finding that severe stressful life events had a fourfold weaker impact on recurrent episodes. The paradox might result from mild stressful life events triggering an episode in persons with a history of depression, a process that would remove persons from the population at risk before a severe stressful life event occurs.

A minority of episodes (7.2%) were not preceded by any of the risk factors studied, and a substantial proportion (21.7%) by only one risk factor. Vascular and other organic degenerative changes might account for episodes that are not well accounted for by psychosocial risk factors (30, 31).

Clinical Implications

Depressogenic stressful life events in later life frequently involve or result from loss of capacities, close ties, and social contacts. Many of these losses are unavoidable, but help in reducing their psychological impact and in finding alternative sources of well-being might be feasible. Hence, treatment and prevention should target appraisal, coping, and compensatory mechanisms (32). These efforts should focus on those with high levels of neuroticism and/or long-term difficulties because they are at the highest risk. Psychosocial approaches combined with antidepressant medication appear to be effective in mitigating the risk of recurrence, even in the very old (31).

Conclusions

This study broadly demonstrated the usefulness of the dynamic stress-vulnerability model (2, 5, 11) as a framework for understanding the etiology of depressive episodes in older community-dwelling people. Although no etiological discontinuity was found between subsyndromal and major episodes, recurrent episodes—compared to first episodes—occur more frequently in persons with high earlier neuroticism levels, by which even mild stressful life events can trigger an episode. As far as vulnerability reflects scarring by earlier episodes, it is important to identify what in the experience of a depressive episode contributes most to the accumulation of vulnerability and how it is expressed.

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References

1. Murphy E: Social origins of depression in old age. Br J Psychiatry 1982; 141:135–142
2. Brown GW, Harris TO (eds): Life Events and Illness. London, Unwin Hyman, 1989
3. Ormel J, Wohlfarth TD: How neuroticism, long-term difficulties, and changes in quality of life affect psychological distress: a longitudinal approach. J Pers Soc Psychol 1991; 60:744–755
4. Paykel ES: Life events, social support and depression. Acta Psychiatr Scand Suppl 1994; 377:50–58
5. Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ: The prediction of major depression in women: toward an integrated etiologic model. Am J Psychiatry 1993; 150:1139–1148
6. Duggan C, Sham P, Lee A, Minne C, Murray R: Neuroticism: a vulnerability marker for depression: evidence from a family study. J Affect Disord 1995; 35:139–143
7. Cloninger CR, Przybeck TR, Svrakic DM: The Temperament and Character Inventory (TCI): A Guide to Its Development and Use. St Louis, Washington University, Center for Psychobiology of Personality, 1994
8. Clayton PJ, Ernst C, Angst J: Premorbid personality traits of men who develop unipolar or bipolar disorders. Eur Arch Psychiatry Clin Neurosci 1994; 243:340–346
9. Krueger RF, Caspi A, Moffitt TE, Silva PA: Personality traits are differentially linked to mental disorders: a multitrait-multidiagnosis study of an adolescent birth cohort. J Abnorm Psychol 1996; 3:299–312
10. Fergusson DM, Horwood LJ: Vulnerability to life events exposure. Psychol Med 1987; 17:739–749
11. Ormel J, de Jong A: On vulnerability to common mental disorders: an evidence-based plea for a developmental perspective, in Common Mental Disorders in Primary Care. Edited by Tansella M, Thornicroft G. London, Routledge, 1999, pp 34–52
12. Bolger N, Schilling EA: Personality and the problems of everyday life: the role of neuroticism in exposure and reactivity to daily stressors. J Pers 1991; 59:355–386
13. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ: Stressful life events, genetic liability and onset of an episode of major depression in women. Am J Psychiatry 1995; 152:833–842
14. Ormel J, Stewart R, Sanderman R: Personality as modifier of the life change-distress relationship: a longitudinal modelling approach. Soc Psychiatry Psychiatr Epidemiol 1989; 24:187–195
15. Kessler RC, Zhao S, Blazer DG, Swartz M: Prevalence, correlates and course of minor depression and major depression in the National Comorbidity Survey. J Affect Disord 1997; 45:19–30
16. Kendler KS, Gardner CO: Boundaries of major depression: an evaluation of DSM-IV criteria. Am J Psychiatry 1998; 155:172–177
17. Judd LL, Akiskal HS, Paulus MP: The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J Affect Disord 1997; 45:5–17
18. Van den Berg MD, Oldehinkel AJ, Brilman EI, Bouhuys AL, Ormel J: Correlates of symptomatic, minor and major depression in the elderly. J Affect Disord 2000; 60:87–95
19. Frank E, Anderson B, Reynolds CF, Ritenour A, Kupfer DJ: Life events and the research diagnostic criteria endogenous subtype: a confirmation of the distinction using the Bedford College methods. Arch Gen Psychiatry 1994; 51:519–524
20. Brown GW, Harris TO, Hepworth C: Life events and endogenous depression: a puzzle reexamined. Arch Gen Psychiatry 1994; 51:525–534
21. Ormel J, Kempen GIJM, Deeg DJH, Brilman EI, van Sonderen E, Relyveld J: Functioning, well-being and health perception in late middle aged and older people: comparing the effects of

depressive symptoms and chronic medical conditions. J Am Geriatr Soc 1998; 46:39–48
22. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO: Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982; 83: 37–49
23. World Health Organization: SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Geneva, WHO, 1992
24. Brown GW, Harris TO: Social Origins of Depression: A Study of Psychiatric Disorder in Women. London, Tavistock, 1978
25. Brilman EI, Ormel J: Life Events, Difficulties and Onset of Depression in Later Life. Groningen, the Netherlands, University of Groningen, Department of Psychiatry, 2000
26. Eysenck SBG, Eysenck HJ, Barrett P: A revised version of the psychoticism scale. Personality and Individual Differences 1985; 6: 21–29
27. Darroch J: Biologic synergism and parallelism. Am J Epidemiol 1997; 145:661–668
28. Kendler KS, Karkowski-Shuman L: Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? Psychol Med 1997; 27:539–547
29. Post RM: Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992; 149:999–1010
30. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M: Clinically defined vascular depression. Am J Psychiatry 1997; 154:562–565
31. Reynolds CF III, Dew MA, Frank E, Begley AE, Miller MD, Cornes C, Mazumdar S, Perel JM, Kupfer DJ: Effects of age at onset of first lifetime episode of recurrent major depression on treatment response and illness course in elderly patients. Am J Psychiatry 1998; 155:795–799
32. Steverink N, Lindenberg S, Ormel J: Towards understanding successful aging: patterned change in resources and goals. Aging and Society 1998; 18:441–467