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Random-mood interpretation of determinants for major depression

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ABSTRACT

Background. It has recently been proposed that major depression disorder (MDD) may, in a heterogeneous population-based cohort, be interpreted in terms of a random-mood model. Mood fluctuations are thought to result from stressors that occur randomly in time. We have investigated whether this concept also holds for more homogeneous groups, defined by known determinants for MDD, and whether the model's parameters, susceptibility (Z) and relaxation time (T), may be evaluated and used to differentiate between subcohorts.

Method. From a large epidemiological survey, the Netherlands Mental Health Survey and Incidence Study (NEMESIS), data on the duration of MDD were obtained for subcohorts, based on gender, severity of depression, recurrence and co-morbidity with dysthymia, anxiety and somatic disorder, and were compared with random-mood simulation calculations.

Results. Susceptibility, Z, is empirically found to be proportional to incidence and may be identified with a risk ratio. A second scaling rule states the proportionality of mean duration with the product of Z and T. This Z–T classification proves to be more sensitive than conventional significance tests. Notably for men/women and for co-morbid anxiety, differences are seen that have previously gone unnoticed.

Conclusions. Depression may be conceptualized as a disorder resulting from random-mood fluctuations, the response to which is influenced by a large variety of determinants or risk factors. The model's parameters can be evaluated and may be used in differentiating between risk factor-defined subgroups.

INTRODUCTION

Major depressive disorder (MDD) is a common and disabling illness with serious consequences for personal and public life (Murray & Lopez, 1997). In many individuals it may take a chronic course, characterized by remissions and recurrences (Keller *et al*. 1982, 1992; Maj *et al*. 1992; Mueller *et al*. 1996, 1999; Solomon *et al*. 1997; de Graaf *et al*. 2002; Spijker *et al*. 2002, 2004).

We have shown (van der Werf *et al*. 2006) that the time course of MDD may be modelled in terms of a random-mood model. In brief, mood is measured on a linear scale. The units need not be specified but for convenience we refer to them as *munits*. Mood is assumed to result as a response to stressor signals, which are as yet left unspecified but may be viewed as life events. These stressor signals, or stimuli, occur

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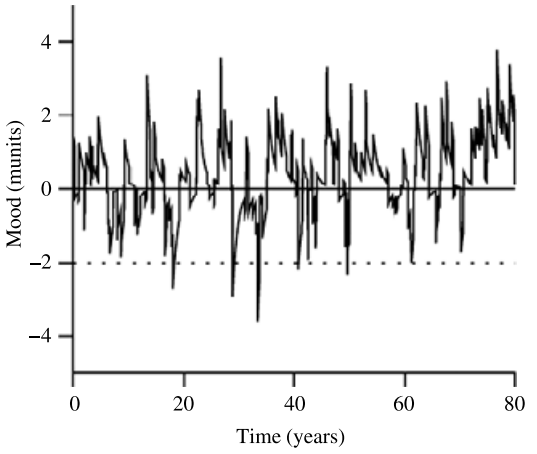


FIG. 1. Mood curve, generated with the random-mood model, as it could be for an arbitrary individual from the general population. The parameters are those for the full NEMESIS cohort: $D = 120$ days, $<T> = 365$ days, $Z = 1$, and depression line $= -2$ munits (broken line).

randomly in time. They can be either positive or negative and their magnitudes are random. Each individual has a different sensitivity to mood stimuli that is reflected in the model's susceptibility parameter, Z, which determines how strongly mood follows the imposed stimulus pattern. Between stimuli, mood is assumed to tend exponentially to zero with a relaxation time, T, which determines how long afterwards the stimulus is felt and how slowly or rapidly it dies out. Aside from this intermittent pattern of stimuli, there are daily mood fluctuations that do not change the essential features of the model. Fig. 1 presents an impression of mood fluctuations as they might occur over a typical lifespan of 80 years. An MDD episode is taken as the time that mood stays below an adopted depression level (broken line in the figure), provided that, in line with the DSM inclusion criteria (APA, 1987), that time is at least 2 weeks.

There has been a tendency over the past decade to interpret individual self-recorded mood sequences in terms of chaos theory, which would suggest that the time development of mood might be deterministic (Gottschalk *et al.* 1995, 1998; Heiby *et al.* 2003). The random-mood model takes an opposite point of view and has been shown to be capable of reproducing the same mood-sequence characteristics (van der Werf *et al.* 2006). Its parameters, Z and T, may be looked upon as characteristic of individual subjects or groups of subjects.

In the present work we attempt to adapt the random-mood model as a tool of analysis and address the following questions:

(1) Does this model also work for subgroups, defined along the lines of several known determinants for depression?
(2) Is it possible to relate the model's parameters, Z and T, to quantities that are easily identified in daily life and/or in clinical practice?
(3) How do contrasting subgroups differ in their values for these parameters?

The data studied are newly originated MDD episodes in a random sample of the Dutch population from the Netherlands Mental Health Survey and Incidence Study (NEMESIS; de Graaf *et al.* 2002; Spijker *et al.* 2002, 2004). Within the follow-up time of 2 years, about 80% of these subjects recover, their depressive fraction decreasing exponentially with a mean duration of approximately 4 months. After the initial 4 months, the full cohort's recovery rate slows down drastically (see also Keller *et al.* 1992). In our data, this later recovery rate was slow enough to make it practical to model the long-lasting fraction ($\approx 20\%$) as constant over the follow-up time. Without suggesting that these subjects could never recover, we call this for ease of reference the chronic fraction.

We examined subgroups based on several known determinants or risk factors, such as comorbidity with other psychiatric and somatic disorders (Keitner *et al.* 1991; Angst, 1996; Swindle *et al.* 1998; de Graaf *et al.* 2002; Iosifescu *et al.* 2004; Spijker *et al.* 2004), severity of index depression (Katon *et al.* 1994; Swindle *et al.* 1998; Spijker *et al.* 2002, 2004), gender (Sargeant *et al.* 1990; Benazzi, 1999; de Graaf *et al.* 2002; Spijker *et al.* 2004) and history of depression (Keller *et al.* 1982; Maj *et al.* 1992; Solomon *et al.* 1997; Mueller *et al.* 1999).

In this work we establish a method by which the random-mood parameters, Z and T, can be evaluated for different risk factor-based subcohorts. The data are organized as survival curves: the percentage of persisting MDDs in a cohort plotted *versus* the time elapsed since their onset. We show that survival curves of the

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more homogeneous risk factor-based subgroups are adequately modelled as an exponentially decaying fraction plus a constant rest group, similar to the full cohort.

The adopted procedure is then used to calibrate simulated random-mood survival curves against exponential decay and to establish their dependence on Z and T.

The results show that: (1) Z may be identified with a risk ratio of the depressed cohort and the general population; and (2) the mean duration of an MDD episode is, apart from a constant, found as the product of Z and T. This Z–T analysis is compared with commonly used tools such as the log rank test and the hazard ratio, and conclusions regarding our current understanding of MDD are discussed.

METHOD

Description of the cohort and subgroups

The data are from NEMESIS (Spijker *et al.* 2002), a prospective psychiatric epidemiological study in the Dutch adult population (7076 subjects, age 18–64 years) conducted in three waves, 1996 (T_0), 1997 (T_1) and 1999 (T_2). From each selected household, one (non-depressive) respondent was chosen randomly; 4796 respondents were examined at all three waves with the Composite International Diagnostic Interview version 1.1 (Smeets & Dingemans, 1993). DSM-III-R (APA, 1987) was used for psychiatric diagnoses. New episodes of major depression (first or recurrent) were found in 273 subjects. Inclusion criteria were: diagnosis of an MDD episode between T_1 and T_2 but no diagnosis of 1-month prevalence between T_0 and T_1. Only first MDD episodes between waves 2 and 3 were used, excluding bipolar disorder and primary psychotic disorder. Using the Life Chart Instrument (LCI; Lyketsos *et al.* 1994), the duration of major depressive episodes was assessed retrospectively in 250 subjects and discretized into 1·5-month intervals. Recovery was defined as no or minimal depressive symptoms in 3 months.

In the present work we studied subgroups for six variables: severity of depression, defined as mild or moderate *versus* severe based on DSM-III-R criteria; co-morbid anxiety disorder, defined as having had any DSM-III-R anxiety disorder between T_1 and T_2; co-morbid dysthymia, defined as having had DSM-III-R dysthymia between T_1 and T_2; somatic co-morbidity, defined as the presence of one or more conditions from a list of 31 somatic disorders for which the subject was treated or monitored by a doctor in the last year before wave 1; history of depression, defined as first *versus* recurrent episodes; and gender.

Details on the random-mood model, survival analysis and significance tests are provided in the Appendix.

RESULTS

Relationship between exponential decay and the random-mood model

Fig. 2(*a*) shows the survival data for the full NEMESIS cohort, compared with exponential decay and a random-mood curve, both in combination with a 20% chronic fraction. The random-mood parameters in this calculation are (van der Werf *et al.* 2006): (1) mean time lapse between successive stimuli, $D=120$ days; (2) depression level $=-2$ munits; (3) $Z=1$; and (4) $T=365$ days, the mean of the Poisson distribution, from which relaxation times are taken. Z and T are obviously individual or group characteristics. To investigate how these influence the mean duration of an MDD, we ran the random-mood program on a grid of Z–T values to produce high-statistics simulated survival curves. D was kept at 120 days and the depression level at -2 munits, thus keeping the stressor pattern unchanged. The resulting curves were subject to a fit with single exponential decay to determine the decay time, τ, which at the same time is the mean duration.

Based on the near-exponential form of the random-mood curves, an approximate empirical scaling is found, as illustrated in Fig. 2(*b*), where mean duration has been plotted *versus* the product ZT. The points cluster around a straight line, at least for $\tau \leqslant 6$ months. As the duration is no longer for any of the subgroups, we have:

Scaling rule A: The decay time, τ, is proportional to the product ZT

For the full cohort, $ZT=12$ months and the decay time is $\tau=3{\cdot}71$ months. This fixes the proportionality constant:

$$ZT=(12/3{\cdot}71)\tau=3{\cdot}235\tau, \qquad (1)$$

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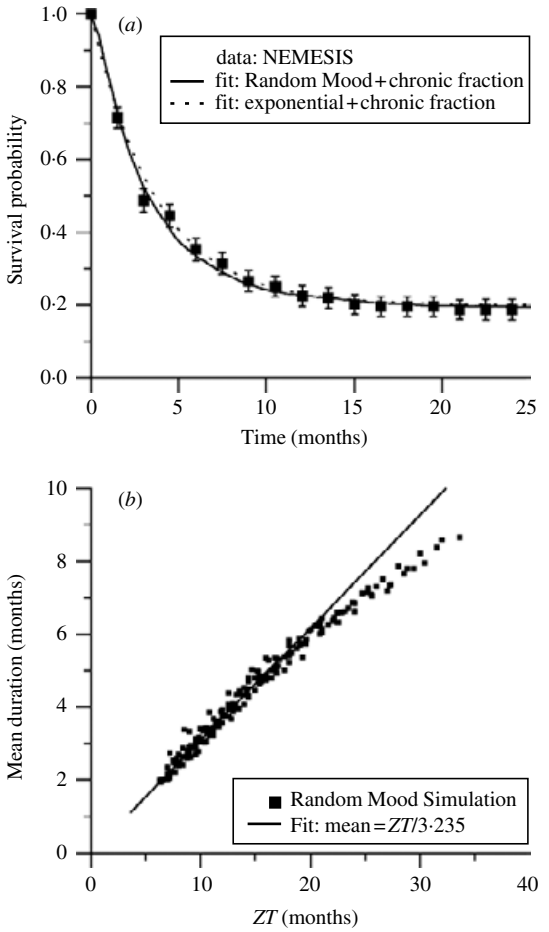


FIG. 2. (*a*) Survival curve of the full NEMESIS cohort, compared with an exponential decay fit (broken line) and with the random-mood model (solid line), both for an 80% recoverable fraction. The 20% long-term fraction, F, has been modelled as constant. The random-mood parameters are those for the general population and are the same as in Fig. 1. (*b*) Decay times obtained from random-mood simulated survival curves (vertical) plotted *versus* the product ZT. The solid line indicates the empirical scaling rule A.

which corresponds to the solid line in Fig. 2(*b*).

Another empirical scaling is observed:

Scaling rule B: Incidence (depressions/year/person) is proportional to Z, independent of T

A simple example illustrates how Z is determined by use of this scaling rule: in the general population, the numbers of men and women are about equal and the probability that a randomly picked individual will be a man or a woman is approximately one-half for both. In the depressed cohort, however, the number of women is about twice that for men. Evidently, the probability that a randomly picked subject, known to be depressed, will be a man is $P(\text{man}^{\text{D}}) \approx 1/3$ and the probability of being a woman, $P(\text{woman}^{\text{D}}) \approx 2/3$. The average susceptibility of the general population can be defined as $Z \equiv 1$. It follows that $Z(\text{man}) \approx (1/3)/(1/2) = 2/3$ and $Z(\text{woman}) \approx (2/3)/(1/2) = 4/3$. This identifies Z as the risk ratio (RR), or likelihood ratio, for identifying an individual as belonging to a certain determinant-defined subgroup, when comparing a depressed cohort with the general population.

The same procedure can be followed for other determinants. In this work we evaluate Z as the ratio for the depressed NEMESIS cohort ($n = 250$, recoverable cases only) and wave 1 ($n = 7076$) of the same study.

The above man/woman example discloses a small ambiguity: the mean susceptibility of the full depressive cohort would be $\langle Z \rangle = (1/3)(2/3) + (2/3)(4/3) = 10/9 = 1{\cdot}11$, rather than $Z = 1$, with which it was analysed. This is not surprising, as the mean susceptibility of a depressed cohort may be expected to be larger than that of the general population. By scaling rule A, the identical mean duration is then obtained by adopting $T = (9/10)12 = 10{\cdot}8$ months. In practice, depending on the bipartition that is chosen, $\langle Z \rangle$ will always be slightly larger than 1, with statistical spread due to the finiteness of the sample.

For some determinants it is impossible to give *a priori* probabilities. An example is severe/non-severe, a distinction that can only be made when the depression already exists. Instead of dropping the analysis altogether, we prefer to proceed on a working assumption, for which we adopt Bayes' postulate of equal *a priori* probabilities (see, for example, Stuart & Ord, 1991). In the particular case of severe/non-severe, this means taking both as 50%. In summary, we have made the important identification:

$$Z(\text{determinant}) = \text{RR}\left(\frac{\text{depressed cohort}}{\text{general population}}\right). \tag{2}$$

Once Z is known, T is obtained by using scaling rule A and equation (1). Hence, these two scaling rules allow for separate estimates of Z and T, which are found to be group-typical parameters.

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Parametric fits of subgroup survival functions

The survival function is taken as a two-parameter form that assumes a chronic fraction F and a reversible part $(1-F)$, with mean duration τ.

$$S(t) = (1-F)\exp(-t/\tau) + F. \quad (3)$$

This may be considered as a limiting case of a double-exponential form, where the second decay time is long enough to make the last term almost constant over the follow-up time. In this form it is similar to multi-exponential forms as used by Von Korff & Parker (1980) and Patten (2002). Modelling the long-term depressive fraction as constant reduces the number of adjustable parameters to just the mean duration, τ, of the recoverable fraction and the size of the chronic fraction, F. Fitting is done by maximizing the likelihood function, which we take in the form as used by Kaplan & Meier (1958).

Survival curves for the different subgroups are shown in Fig. 3(*a*), along with their fits. The fit parameters and their standard deviations are given in Table 1, along with the random-mood parameters, Z and T, that follow from scaling rules A and B.

Fig. 3(*b*) shows a two-by-two comparison of the 95% confidence contours (CCs) for the subgroups that are being contrasted, drawn in the plane of τ and F. From a visual inspection of their distances and the lack of overlap of their CCs, significance is immediately apparent for the risk factors severity, recurrence and dysthymia.

Survey of the significance tests

Various methods exist for testing the null hypothesis, that two different survival curves might result from a common underlying mechanism. Two commonly used statistics are the log rank test and the hazard ratio (HR), which is the output of a univariate Cox regression. Both log rank and HR are χ^2 (df = 1) statistics. In addition, we use a parametric test, based on the differences in the fit parameters τ and F. This statistic, which we denote as W^2, is judged against a χ^2 (df = 2) distribution. Its precise definition, along with a brief description of log rank and HR, is given in the Appendix.

The results for these three test statistics are listed in Table 2. All three tests indicate that the probability for the null hypothesis to be true is outside the 95% confidence interval (CI) for the following cases: (1) non-severe/severe, (2) non-recurrent/recurrent and (3) dysthymia/no dysthymia. For the women/men subgroups the HR and the log rank are well within the 95% CI, but the parametric W^2 test is close to the limit. All methods agree that the difference between somatic disease/no somatic disease is small enough to make the null hypothesis probable even inside the 63% CI. No anxiety/anxiety is within the 95% CI for all three criteria.

Z–T classification of risk factors

Figure 4 shows a plot of Z *versus* τ. On the basis of the three criteria, log rank, HR and W^2, the difference was found to be not or hardly significant for men/women, no somatic disease/somatic disease and no anxiety/anxiety. These criteria judge the difference between subgroups by the shape of their survival curves alone. When taking into account differences in incidence between the subgroups, as in the Z–T classification, very marked differences are evident; depressions in women are classified as high incidence/short duration, while in men they are of low incidence/long duration. The subgroups no anxiety and anxiety have almost identical duration, but the incidence among subjects with co-morbid anxiety is more than two times the average of the general population and three times higher than for subjects without anxiety. For the subgroups with co-morbid somatic disease/no somatic disease, the Z–T classification reveals no significant difference.

DISCUSSION

The present work has demonstrated that survival curves for all subcohorts can be described by a chronic fraction, F, of typically 10–30%, and a reversible fraction $(1-F)$ that decays exponentially, its mean duration varying between 2·0 months (dysthymia) and 5·5 months (severe depression). We have established two empirical scaling rules, through which the exponential decay time can be connected to the random-mood model and by which its parameters Z, susceptibility, and T, relaxation time, can be determined separately. Hence the random-mood model is found to work for all subcohorts, and

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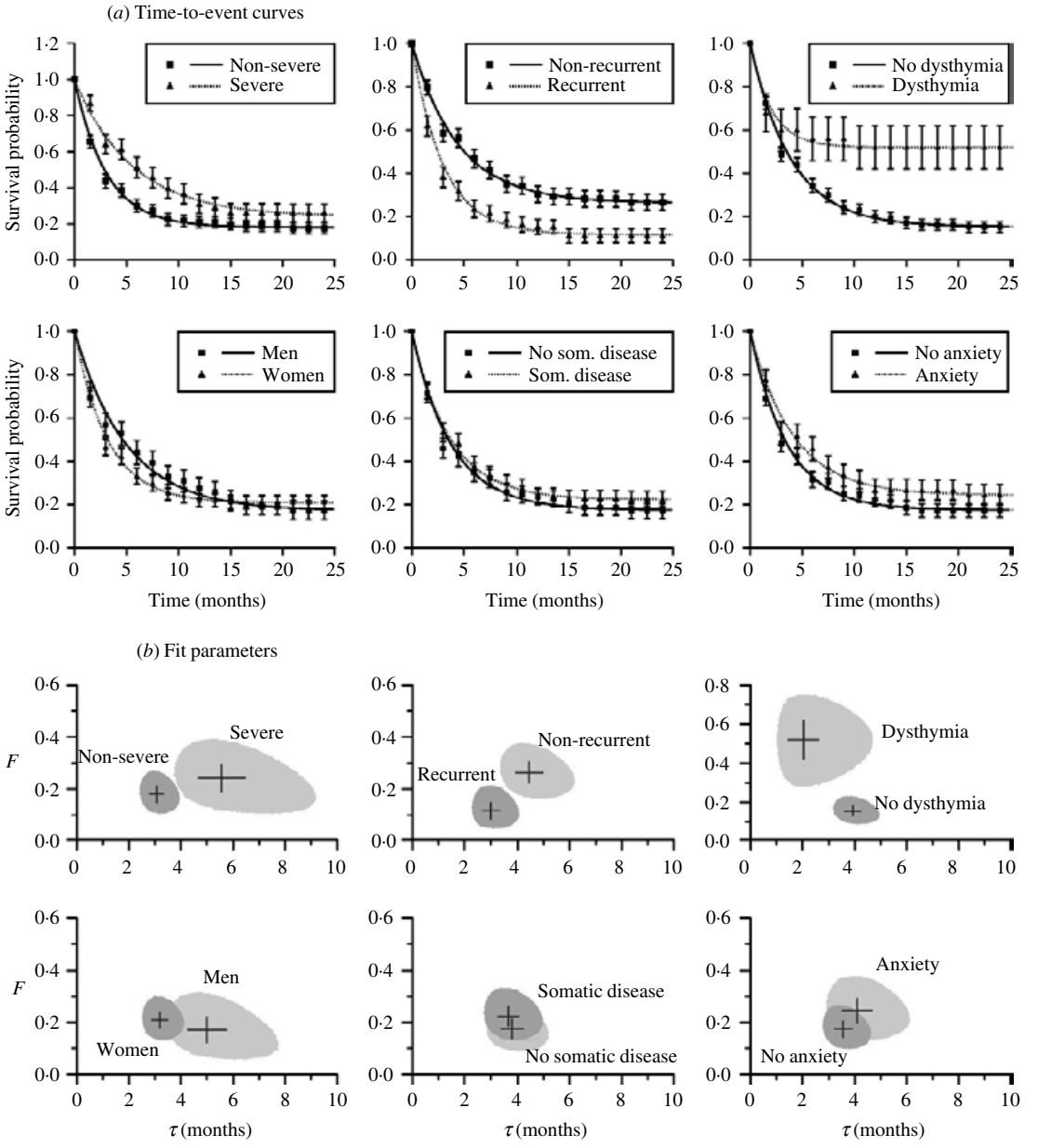


FIG. 3. (*a*) Survival curves for contrasted risk factor-defined subgroups. (*b*) 95% confidence contours (CCs) on the fit parameters of the contrasted groups. τ is the mean duration for the reversible fraction $(1-F)$ and F is the chronic fraction. Crosses indicate standard deviations on the individual parameters τ and F.

each of them is characterized by its own group average values of Z and T.

We have attempted to differentiate between the subgroups in three different ways: (1) by the conventional log rank and HR test; (2) by differences in parametric fits, embodied in our W^2 statistic and visual inspection of the 95% CCs [Fig. 3(*b*)]; and (3) by the Z–T classification, which concentrates on the non-chronic fraction and uses relative incidence as an

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Table 1. *Parametric analysis of the NEMESIS data and subgroups*

Subgroup	% of NEMESIS[a]	*A priori* probability[b] (%)	Z	$T \pm \Delta T$ (months)	$F \pm \Delta F$	$\tau \pm \Delta\tau$ (months)
Total	100	100	1·00	12·00 ± 0·97	0·201 ± 0·028	3·71 ± 0·30
Non-severe	70	50[c]	1·43	6·91 ± 0·94	0·181 ± 0·032	3·06 ± 0·29
Severe	30	50[c]	0·57	31·66 ± 2·98	0·242 ± 0·054	5·56 ± 0·92
Non-recurrent	57	50[c]	1·05	13·67 ± 1·71	0·264 ± 0·041	4·44 ± 0·53
Recurrent	43	50[c]	0·95	10·22 ± 1·07	0·118 ± 0·033	3·00 ± 0·33
No dysthymia	90	97	0·97	13·05 ± 1·07	0·154 ± 0·027	3·93 ± 0·33
Dysthymia	10	3	1·74	3·76 ± 1·94	0·520 ± 0·100	2·03 ± 0·60
Men	33	47	0·73	22·15 ± 2·43	0·172 ± 0·050	5·00 ± 0·75
Women	67	53	1·24	8·32 ± 1·00	0·209 ± 0·033	3·18 ± 0·31
No somatic disease	47	49	1·00	12·22 ± 1·42	0·175 ± 0·038	3·78 ± 0·44
Somatic disease	53	51	1·00	11·78 ± 1·33	0·224 ± 0·040	3·64 ± 0·41
No anxiety	66	86	0·79	14·62 ± 1·13	0·175 ± 0·033	3·55 ± 0·35
Anxiety	34	14	2·37	2·37 ± 1·91	0·245 ± 0·049	4·09 ± 0·59

NEMESIS, The Netherlands Mental Health Survey and Incidence Study; Z, susceptibility (random-mood parameter), obtained from scaling rule B; T, relaxation time (random-mood parameter), obtained from scaling rule A; F, long-lasting (chronic) fraction; τ, mean duration for recoverable fraction.

[a] Percentage of depressive NEMESIS cohort ($n = 250$).

[b] *A priori* probability among the general population, estimated from wave 1 ($n = 7076$).

[c] Assuming Bayes' hypothesis of equal *a priori* probabilities.

Table 2. *Significance tests for contrasted subcohorts*

	Hazard ratio test			Log rank test		Parametric test	
Subgroup 1/subgroup 2	HR	95% CI	p	Log rank	p	W^2	p
Non-severe/severe	0·67	0·49–0·89	0·001	7·47	0·006	7·7	0·021
Non-recurrent/recurrent	1·63	1·26–2·11	0·003	15·02	<0·001	13·0	0·002
No dysthymia/dysthymia	0·47	0·24–0·79	<0·001	9·08	0·003	20·2	<0·001
Women/men	0·91	0·68–1·19	0·480	0·25	0·617	5·4	0·067
No somatic disease/somatic disease	0·90	0·69–1·16	0·395	0·64	0·424	0·84	0·657
No anxiety/anxiety	0·81	0·61–1·07	0·098	2·39	0·122	2·0	0·368

HR, Hazard ratio; CI, confidence interval.

Log rank test: Mantel–Cox form (df = 1). Parametric test: W^2 is a χ^2 (df = 2) statistic. See Appendix.

additional tool. This Z–T classification appears to have a definite added value and brings out pronounced differences in men/women and anxiety/no anxiety, which the more conventional criteria do not or hardly detect.

In the following sections we survey the current understanding of the three characteristics, chronicity, duration and incidence, for the different risk factors.

Severe/non-severe depression

All three test statistics judge the difference between these subgroups significant outside the 95% CI. The mean duration for the severe cases is much longer than for the non-severe cases: 5·56 *v.* 3·06 months. In addition, the risk that the depression will become long-lasting is larger in severe depressions. The random-mood Z–T classification finds that severe depressions are of long duration and non-severe depressions of short duration. As severity is measured by the number of symptoms at baseline, these outcomes are entirely as expected and in agreement with existing literature (Katon *et al.* 1994; Swindle *et al.* 1998; Spijker *et al.* 2002, 2004; Barkow *et al.* 2003).

Recurrent/non-recurrent depression

The difference between the survival curves of these groups is found outside the 95% CI for all three test statistics. Recurrent depressions have shorter duration than first depressions, 3·00 *v.* 4·44 months, while the probability of developing into a long-lasting depression is also smaller.

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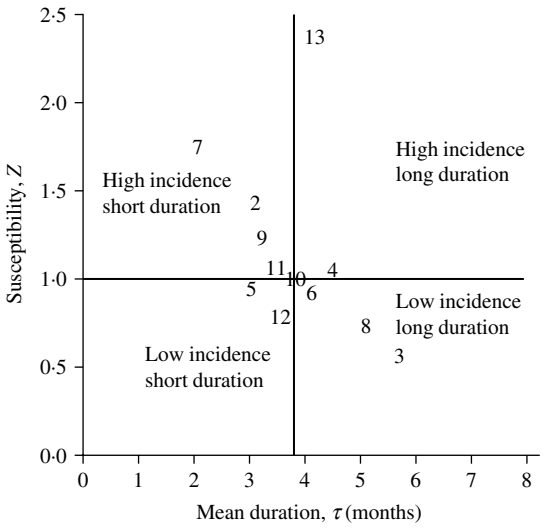


FIG. 4. Classification by susceptibility, Z, and mean duration, τ. The numbers correspond to the subgroups shown in Tables 1 and 2: (1) total, (2) non-severe, (3) severe, (4) non-recurrent, (5) recurrent, (6) no dysthymia, (7) dysthymia, (8) men, (9) women, (10) no somatic disease, (11) somatic disease, (12) no anxiety, (13) anxiety.

It is not intuitively evident why recurrent depressions should be shorter than non-recurrent ones. Ormel *et al.* (2001) have suggested that such depressions could be due to general vulnerability. In the language of the random-mood model, this would suggest that the subject has high susceptibility and that consequently the stressors must have short relaxation times. We have based our Z–T classification on Bayes' postulate of equal *a priori* probabilities, resulting in the near-average values $Z = 0{\cdot}95$ and $T = 10{\cdot}22$ months. Considering, however, that scaling rule A determines only their product, high susceptibility combined with short relaxation time is indeed a valid scenario.

No dysthymia/dysthymia

At only 10% of the total cohort, the dysthymia subgroup has a very different signature: the chronic fraction is large (52%), but for the recoverable part, the duration is short (2·03 months). All three test statistics indicate that the survival curves are significantly different beyond the 95% CI. In terms of the Z–T classification, the recoverable part of the dysthymia group is characterized as of high susceptibility and short duration. Dysthymia is a prolonged state of low baseline mood, in which it meets a minimum number of inclusion criteria (APA, 1987) that are in common with those for MDD, but fewer in number. When the number of inclusion symptoms increases temporarily to above the diagnostics level of MDD, the dysthymic subject is said to have a double depression. This is the situation we are considering here. In a random-mood interpretation, dysthymia might be characterized as a state of reduced distance between baseline mood and depression level, which might then be triggered by small-amplitude stimuli. This hypothesis provides a natural explanation for the high susceptibility found in our Z–T classification (Table 1, Fig. 4). It does not, however, without further assumptions, explain the very short duration of the recoverable depressive episodes (only 2·03 months). This short duration suggests that the stimuli themselves should have a reduced relaxation time, T. Both aspects might be explained by a 'selective response' scenario: a dysthymia patient might have (very) long relaxation times for strong negative stimuli, causing these to pile up to a negative level, which is, however, still subthreshold for MDD. For small negative stimuli the patient might then show 'normal' responses. In addition, impairment between coping with positive and negative daily events, one of the inclusion criteria for dysthymia, may further lower the baseline mood level.

Women/men

No major differences in survival curves for men and women are found by the HR and log rank tests. The parametric W^2 statistic is, however, at the edge the 95% CI. The difference between men and women is even more evident from the Z–T classification: about two-thirds of the full cohort are women and one-third are men. This translates into a two-times higher susceptibility for women. Although the difference between men and women in their risk of becoming depressed is generally known, some studies find no significant difference in duration and chronicity (Eaton *et al.* 1997; Simpson *et al.* 1997; Spijker *et al.* 2002, 2004) while others do (Sargeant *et al.* 1990). In hospitalized subjects, chronicity has been observed to be more frequent in women than in men (Keitner *et al.* 1991). In our study we found only a slightly higher chronic fraction for women. However, the mean duration for the recovering cases is very different: 3·18 months

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for women *versus* 5·00 months for men. This is the more remarkable because the fraction of women with severe depression characteristics at baseline is 34% compared with only 23% for men [odds ratio (OR) 1·70, $p=0·051$]. Oldehinkel *et al*. (2000) suggested that women, once depressed, are better at putting positive life changes into effect and thus are better able than men to overcome depression. In our cohort, the percentage of women with co-morbid anxiety disorder was significantly higher than for men: 39% *v*. 23% (OR 2·15, $p=0·004$). Recurrence was also found more frequently in women than in men (46% *v*. 36%, OR 1·50, $p=0·094$), unlike the results of the study by Eaton *et al*. (1997), who found no difference in recurrence.

No somatic disease/somatic disease

None of the three test statistics indicate a significant difference between the two survival curves. Neither does the *Z–T* classification. This is not surprising because, for the most prevalent diseases included in the criterion list (hypertension, sinusitis, back pain and asthma), their possible association with depression has not been demonstrated. Diseases that are known risk factors (Evans *et al*. 2005), such as cardiovascular disease, diabetes mellitus, AIDS/HIV, cancer and rheumatoid arthritis, account for less then 20% of the prevalence in the present subcohort. Even when assuming a 50% increase in duration in such cases, the net effect on the full subcohort will only be some 10%. This is in line with the observed 7% higher median duration of $3·76\pm0·54$ months for the diseased group *versus* $3·52\pm0·49$ months for the non-diseased subcohort and the 30% higher long-duration (chronic) fraction of $0·224\pm0·040$ as compared to $0·175\pm0·038$.

No anxiety/anxiety

The survival curves for no anxiety/anxiety do not differ significantly as judged by the log rank and HR criteria and by the W^2 test. The *Z–T* classification, however, reveals a remarkable difference: anxiety is associated with a very high susceptibility for becoming depressed, by far the highest of all the risk factors investigated in this study. Several studies (Wittchen *et al*. 2003; Spijker *et al*. 2004) have reported a negative effect of anxiety on the course of depression. Our investigation confirms this: we find that anxiety is more likely to lead to chronicity and also the duration for the recoverable cases is slightly higher. From subject numbers at baseline, anxiety is found to correlate strongly with co-morbid dysthymia (OR 2·76, $p=0·013$) and with gender, where it affects women more often then men (OR 2·15, $p=0·004$). In subjects with anxiety disorder, severe depression is observed almost twice as frequently as in subjects without anxiety (OR 2·49, $p<0·001$). These correlations suggest that anxiety may be viewed as an important cause of increased incidence and that it has an aggravating effect on severity. No significant correlation with recurrence was observed (OR 0·82, $p=0·406$).

CONCLUSION

Our present work further supports the conceptualization of depression as a response to randomly occurring stressors. It provides an explanation of how risk factor-defined groups of individuals may differ in their susceptibility and response time to stressors. A detailed analysis of survival data on depression, including data on relative incidence, has demonstrated the feasibility of evaluating the group-typical random-mood model parameters susceptibility and relaxation time and has established their connection with the easy-to-interpret observables risk ratio and mean duration. This *Z–T* classification has definite merits: in the present work it highlights differences in incidence and in the typical time course of depression between men and women, and between subjects with and without co-morbid anxiety, that have previously gone unnoticed. By combining information on incidence and duration for a given determinant, the *Z–T* classification differs from the Cox regression, which uses determinants to parameterize the time course of MDD, but not its incidence.

APPENDIX: METHODS OF ANALYSIS

Random-mood model

Day-to-day mood sequences, y_m, are generated by (van der Werf *et al*. 2006):

$$y_m - y_{m-1}\exp(-1/T) = Zg_w(D). \qquad (4)$$

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The component $g_w(D)$ is gaussian white noise: stimuli randomly distributed in time with average spacing D. Z is the susceptibility and T the relaxation time. It is easiest to think of $g_w(D)$ as expressed in munits. Z is then just a number, which agrees with equation (2), where Z has been identified with a risk ratio. The random-mood simulation that matches the recoverable fraction of the full NEMESIS cohort is obtained by taking $D=120$ days, $Z\equiv 1$, relaxation times Poisson-distributed with mean $\langle T\rangle = 365$ days, and a depression line at -2 munits.

Non-parametric estimates and significance tests

At each follow-up inspection, numbered by k, we denote the number of subjects at risk as n_k and those whose MDD episode has ended during the last interval, as m_k. The model-independent estimate (Kaplan & Meier, 1958) for the *conditional probability* that MDD will survive the kth interval, while already having lasted during all previous ones, is $\hat{p}_k=(n_k-m_k)/n_k$. Its complement is the *hazard*: $\hat{h}_k=m_k/n_k$. Conventionally, circumflexes are used to indicate that these are non-parametric estimates, based directly on the data. The *survival probability* is evaluated as the product $\hat{S}_k=\hat{p}_1\hat{p}_2,\ldots,\hat{p}_k$. It is also known as a *time-to-event* curve. In our case, the looked-for event is the end of an MDD episode. When comparing two different survival curves, the corresponding hazards are written as $\hat{h}_{jk}=m_{jk}/n_{jk}$ $(j=1, 2)$. The commonly used log rank test compares the total number of events in subgroup 1 against the number expected if, instead of $\hat{h}_{1k}=m_{1k}/n_{1k}$, which are the estimates of the first group on its own, the estimates of the combined group $(m_{1k}+m_{2k})/(n_{1k}+n_{2k})$, would have been used. A univariate Cox regression assumes the hazards of the two groups to be just scaled versions of one another: $h_{2k}=Ah_{1k}$. The value of A for which this procedure gives the highest likelihood is called the hazard ratio (HR). Both the log rank and the hazard ratio only probe the global similarity or dissimilarity of two survival curves. For further details, the reader is referred to a text-book (e.g. Kleinbaum, 1996).

Parametric significance test

Survival curves are of the form: $S(t)=(1-F)\exp(-t/\tau)+F$. Consider fits for two subgroups, $\tau(1)$, $F(1)$ and $\tau(2)$, $F(2)$, and their standard deviations (SD). Differences between the curves may be judged by a properly weighted distance in the (τ, F) plane [see Fig. 3(*b*)]. To this end, Wald statistics are formed: $W(\tau)=(\tau_1-\tau_2)/\mathrm{SD}(\tau_1-\tau_2)$ and $W(F)=(F_1-F_2)/\mathrm{SD}(F_1-F_2)$. The quantity $a=[W^2(\tau)-2\rho W(\tau)W(F)+W^2(F)]/(1-\rho^2)$ may be shown to follow a χ^2 (df$=2$) distribution. We estimated the distribution correlation coefficient, ρ, from simulated random-mood data and found it to be very small: $\rho\approx -0{\cdot}017$. Thus $W(\tau)$ and $W(F)$ are highly uncorrelated and the quantity $W^2\equiv W^2(\tau)+W^2(F)$ can serve as a χ^2 (df$=2$) test statistic of the null hypothesis.

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DECLARATION OF INTEREST

None.

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