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ORIGINAL PAPER

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Lifetime depressive and somatic symptoms as preclinical markers of late-onset depression

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Abstract *Background* Several risk factors of depression, i. e., female gender and life-stress, have been identified. Few studies have focussed on symptoms as preclinical markers of depression. In these studies current symptoms like dysphoria, tiredness and increased appetite predicted later depression. Even though of possible interest for treatment, no study focussed on lifetime symptoms as preclinical markers of depression. Consequently, we examined lifetime depressive and somatic symptoms with respect to later development of late-onset depression. *Methods* 664 non-depressed elderly subjects without lifetime diagnoses of depression at the initial examination were selected for a prospective follow-up study (mean follow-up ± SD: 5.02 ± 2.44 years). 51 subjects (mean age ± SD: 66.6 ± 11.3) developing late-onset depression (defined as depression starting after age 60) were compared to those remaining non-depressed (mean age ± SD: 59.1 ± 16.0) during follow-up using the CIDI. To determine the influence of lifetime symptoms on the development of depression, chi-square statistics and multivariate logistic regression analyses were performed. *Results* The following symptoms being present over a period longer than two weeks were individual preclinical markers of late-onset depression: dysphoria, increased appetite, insomnia, lack of energy, morning depth, lack of joy and interest, inferiority feeling, lack of self-confidence, poor concentration, indecisiveness, thinking about death, wish to die and joint pain. The most important symptoms elevating the risk of late-onset depression in a multivariate model were lack of joy and interest, poor concentration, increased appetite, lack of energy and joint pain. *Conclusions* Different symptoms can be used individually and in combination to predict later depression. This might allow early treatment.

Key words lifetime symptoms · late-onset depression · preclinical markers · follow-up study

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Introduction

Depression is described as a continuum ranging from a few symptoms to major depression (Solomon et al. 2001). Angst et al. (1997) described a continuous course from multiple subthreshold manifestations to major depression. Previous subthreshold depression increases the risk of later major depression (Parker et al. 1998). Many subjects experience clinically significant symptoms, which are below the threshold for major depression (Sherbourne et al. 1994), but which might be used for an early diagnosis or prediction of depression.

Different risk factors of depression, i. e., female gender (Coryell et al. 1992; van den Berg et al. 2000; Steffens et al. 2000), severe life stress, neuroticism, positive family history (van den Berg et al. 2001) or social factors like marital status (Kivela et al. 1996; Bertakis et al. 2001; Patten, 2001), have been identified, but there is no study about lifetime depressive or somatic symptoms as possible preclinical markers of late-onset depression. Few authors examined current symptoms – defined as being present in the previous two weeks – as risk factors of later depression: an elevation of the risk of major depression in subjects showing current depressive symptoms one year (Horwath et al. 1992) or 3.6 years before (Henderson et al. 1997) was reported. Berger et al. (1998) identified dysphoria and appetite disturbance as specific symptoms predicting later depression. According to Barkow et al. (2001), pain, tiredness, dysphoria, agitation, increased appetite and feelings of worthlessness increased the risk of depression one year later in primary health care samples. However, none of these authors investigated lifetime symptoms as preclinical markers of

later depression. Focussing on current symptoms may be less useful for assessing all previous and possibly intermittent symptoms of depression than focussing on lifetime symptoms for several reasons:

- The subject might experience a short time without depressive or somatic symptoms or be partially recovered at the time of the examination.
- The subjects' symptoms might vary from episode to episode.

Thus, lifetime symptoms give a more comprehensive phenomenological picture of the disorder.

In addition to depressive symptoms, somatic symptoms might be preclinical markers of depression, because somatic diseases, i. e., gastrointestinal disorders (van Marwijk et al. 1996) or chronic pain (Gallagher et al. 1999), may cause depression and vice versa. Some patients report somatic symptoms like back or chest pain, headache or myalgia instead of depressive symptoms (Corruble et al. 2000; Simon et al. 1999).

Consequently, the present prospective follow-up study intends to reveal the role of lifetime depressive and somatic symptoms as preclinical markers of late-onset depression. Symptoms for depression according to DSM-III-R criteria (American Psychiatric Association, 1987), which have been present for at least 14 days during lifetime, and symptoms of somatic diseases (see Table 2) – selected according to previous publications describing an association between somatic diseases and depression (van Marwijk et al. 1996; Gallagher et al. 1999; Burg et al. 2001) and appearing with rates above 15 % in our sample – were examined.

Methods

Recruitment of subjects for initial and follow-up examination

Participants were initially recruited in the scope of a family study investigating the familial co-aggregation of dementia, depression and other psychiatric disorders in the elderly. Recruitment strategies and results of the initial family study have already been published (Heun et al. 1995, 2001). Briefly, patients with Alzheimer's disease (AD) and/or major depression (according to DSM-III-R criteria) aged 60 or older were consecutively recruited from the Departments of Psychiatry of the University of Mainz (recruitment from 1992 to 1995) and of the University of Bonn (recruitment from 1996 to 1998). Control subjects who were group-matched to the patient sample for age, gender, and educational background were recruited with the support of the cities' census agencies. The patients and controls were asked to provide names and addresses of all first-degree relatives. For the purpose of the family study, patients and controls had to have at least one first-degree relative aged 55 or older who was available for an interview. The final sample included 78 subjects with AD, 78 with early-onset depression, 74 with late-onset depression (onset age > 60 years), and 53 with histories of both AD and depression (comorbid patients) and 162 control subjects from the general population. The 445 personally interviewed study subjects had 3002 first-degree relatives. Information on 210 (7 %) of these relatives was unavailable. Of the remaining 2792 relatives, 1236 (44.3 %) were deceased. Thus 775 (49.8 %) of the remainder could be interviewed.

For the follow-up examination, which was carried out from 1999 to 2001 in Mainz and Bonn, all subjects older than 55 years of age at the initial family study were selected. Subjects were contacted by mail and phone and asked for participation in a personal interview. The study was approved by the local ethic committees and all participants gave written informed consent.

A total of 664 elderly subjects (having participated in both examinations) without lifetime diagnoses of depression according to DSM-III-R criteria or other psychiatric disorders at the initial personal interview was selected for the present follow-up study. Consequently, patients with major depression and Alzheimer's disease recruited for the initial examination and patients younger than 55 years of age at the follow-up examination were excluded from the present sample. Excluding subjects with lifetime psychiatric disorders was necessary to prevent confounding of results by other symptoms of psychiatric disorders that are similar to those of depression.

The mean age of this sample at the initial examination was 59.7 ± 15.89 years (mean ± SD). The duration of follow-up was 5.02 ± 2.44 years (mean ± SD).

Diagnoses

All subjects were initially interviewed using the Composite International Diagnostic Interview (CIDI; WHO, 1990), which permits DSM-III-R diagnoses for major psychiatric disorders. During the interview subjects were asked, whether symptoms of psychiatric disorders and somatic symptoms had appeared at any time of their lives lasting for more than two weeks. The symptoms had to be serious enough to seek medical help.

At the follow-up examination the CIDI or alternatively family history information (Andreasen et al. 1977) was applied. The family history method was used to obtain more diagnostic information on subjects with psychiatric disorders, because those subjects are more often unavailable for an interview than healthy subjects (Heun et al. 1995). Therefore, to prevent selection bias, family history information on unavailable subjects is necessary. Validity and reliability of the family history method have been described previously (Heun et al. 1996; Heun et al. 1998a; Heun et al. 1998b; Ptok et al. 2001).

Subjects were interviewed by medical students in their final years of training after a four-week clinical clerkship on a psychiatric ward or by junior physicians. All interviewers were comprehensively trained including ten supervised interviews. The interviewers were not informed about the subjects' diagnoses to prevent awareness bias. The final diagnoses were made using the best-estimate procedure (Leckman et al. 1982). Two experienced psychiatrists who were not informed about the identity of the subjects had to agree on a diagnosis. The lifetime diagnoses were made according to DSM-III-R. The diagnosis of major depression included the DSM-III-R codes 296.20 to 296.36 to obtain a homogeneous group of 51 depressed subjects.

Late-onset depression was diagnosed when the age at onset was above 60 years. This threshold was chosen in accordance with different publications (Burvill et al. 1989; Maier et al. 1991; Greenwald et al. 1996; Reynolds et al. 1998). Of the subjects, 613 remained non-depressed according to DSM-III-R criteria; 51 initially non-depressed subjects had developed at least one episode of depression during the follow-up period (5 years) after the age of 60 years. Most of these episodes were already remitted (n = 44), only seven subjects still suffered a major depressive episode at the follow-up examination. Thus, the point prevalence of depression at follow-up was 1.1 %. A detailed description of the present sample is given in Table 1.

Independent and dependent variables

The dependent variable of the present study was the development of late-onset depression during follow-up. Independent variables were the presence of lifetime symptoms of depression and somatic diseases (Table 2). Additional independent variables were age, gender, educational level, number of children and marital status as important sociodemographic factors. These variables were inserted in the logistic regression analysis.

Table 1 Description of 664 subjects without the lifetime diagnosis of depression at the initial examination

	Subjects remaining non-depressed during follow-up	Subjects becoming depressed during follow-up	Group comparison (T-test or χ^2-test)
N	613	51	
Age (years ± standard deviation)	59.1 ± 16.0	66.6 ± 11.3	T = 3.27, df = 662, p = 0.001
Gender (% female)	53.8%	64.7%	χ^2 = 2.25, df = 1, p = 0.134
Number of children (N; mean ± SD)	1.8 ± 1.6	2.1 ± 1.3	T = 1.29, df = 662, p = 0.198
Education (years in school ± SD)	10.0 ± 2.3	9.5 ± 2.3	T = −1.23, df = 509, p = 0.221
Marital status (% married)	69.8%	66.7%	χ^2 = 0.22, df = 1, p = 0.651
Duration of follow-up (years ± SD)	5.04 ± 2.5	4.8 ± 2.4	T = −0.61, df = 662, p = 0.542

Table 2 Univariate analysis showing the importance of depressive symptoms and symptoms of somatic diseases as preclinical markers of late-onset depression

Category (depressive symptoms)	Symptom	Odds Ratio	95% CI	χ^2 Statistics
Mood	Dysphoria	2.48	1.38–4.45	χ^2 = 9.79; df = 1; p = 0.002
Appetite	Loss of appetite	2.13	0.99–4.61	χ^2 = 3.88; df = 1; p = 0.080*
	Increased appetite	2.80	1.17–6.69	χ^2 = 5.81; df = 1; p = 0.016*
Sleep	Difficulty falling asleep	2.40	1.28–4.52	χ^2 = 7.87; df = 1; p = 0.005
	Frequent awakenings during night	1.88	1.02–3.47	χ^2 = 4.17; df = 1; p = 0.041
	Early morning awakening	2.02	0.94–1.04	χ^2 = 3.31; df = 1; p = 0.069
	Hypersomnia	1.43	0.32–6.38	χ^2 = 0.23; df = 1; p = 0.651*
Tiredness	Lack of energy	2.98	1.54–5.79	χ^2 = 11.3; df = 1; p = 0.001
	Morning depth	3.70	1.92–7.13	χ^2 = 17.1; df = 1; p < 0.001
Psychomotor disturbance	Slowing of movement	2.07	0.59–7.27	χ^2 = 1.34; df = 1; p = 0.213*
	Agitation	3.40	1.08–10.7	χ^2 = 4.95; df = 1; p = 0.050*
Interest	Lack of joy and interest	5.02	1.71–14.7	χ^2 = 10.5; df = 1; p = 0.009*
Worthlessness	Worthlessness, guilt, sin	3.18	1.02–9.90	χ^2 = 4.43; df = 1; p = 0.059*
	Inferiority feeling	3.75	1.57–9.15	χ^2 = 9.58; df = 1; p = 0.008*
	Lack of self-confidence	3.14	1.23–8.05	χ^2 = 6.27; df = 1; p = 0.025*
Cognition	Poor concentration	4.05	1.93–8.51	χ^2 = 15.7; df = 1; p = 0.001*
	Slowing of thinking	2.74	0.58–13.1	χ^2 = 1.75; df = 1; p = 0.204*
	Indecisiveness	4.98	1.86–13.4	χ^2 = 12.3; df = 1; p = 0.004*
Suicidal ideation	Thinking about death	2.14	1.14–4.00	χ^2 = 5.87; df = 1; p = 0.015
	Wish to die	3.59	1.39–9.30	χ^2 = 7.82; df = 1; p = 0.015*
	Suicidal thoughts	0.52	0.12–2.19	χ^2 = 0.83; df = 1; p = 0.568*
	Attempted suicide	n. a.	n. a.	χ^2 = 0.67; df = 1; p = 1.000*
Pain	Abdominal pain	1.42	0.79–2.55	χ^2 = 1.37; df = 1; p = 0.243
	Back pain	0.92	0.52–1.63	χ^2 = 0.09; df = 1; p = 0.766
	Joint pain	2.16	1.18–3.94	χ^2 = 6.47; df = 1; p = 0.011
	Chest pain	1.01	0.48–2.14	χ^2 = 0.01; df = 1; p = 0.979
	Headache	1.09	0.60–1.96	χ^2 = 0.08; df = 1; p = 0.783
Gastrointestinal symptoms	Vomit	1.29	0.61–2.74	χ^2 = 0.44; df = 1; p = 0.510
	Nausea	1.05	0.48–2.30	χ^2 = 0.02; df = 1; p = 0.906
	Diarrhea	0.97	0.46–2.04	χ^2 = 0.01; df = 1; p = 0.928
	Flatulence	1.34	0.72–2.53	χ^2 = 0.85; df = 1; p = 0.356
Cardiopulmonary symptoms	Difficulty in breathing	1.06	0.44–2.57	χ^2 = 0.02; df = 1; p = 0.903
	Heart palpitation	1.09	0.57–2.06	χ^2 = 0.07; df = 1; p = 0.797
	Vertigo	1.50	0.83–2.70	χ^2 = 1.82; df = 1; p = 0.178

* Fisher's exact test

Statistical analyses

To identify predictors of new depression, lifetime symptoms of depression or somatic disease at the initial investigation were compared between subjects suffering at least one major depressive episode during the time span the initial and the follow-up examination and subjects remaining non-depressed. Chi-square statistics and T-tests were used for group comparisons of subjects becoming depressed versus subjects remaining non-depressed. Stepwise forward logistic regression analysis was performed to account for the simultaneous association of lifetime symptoms with the development of depression during follow-up and to account for age differences. To allow comparison with the results of other authors $p < 0.05$ was taken as the threshold for statistical significance. Correlation analyses were used to investigate the association between different depressive symptoms.

Results

Subjects suffering from at least one episode of depression during follow-up and subjects remaining non-depressed did not differ significantly according to gender, marital status, educational level (measured by number of school years), number of children or duration of follow-up, but they differed according to their mean age (Table 1).

Chi-square statistics investigating the influence of individual symptoms on the development of depression during follow-up revealed the following symptoms as preclinical markers of depression: dysphoria, increased appetite, insomnia described as frequent awakenings during the night or difficulty falling asleep, lack of energy and morning depth as signs of tiredness, lack of joy and interest, inferiority feeling, lack of self-confidence, cognitive disturbances like indecisiveness and poor concentration, thinking about death, wish to die and joint pain (Table 2).

The above-mentioned predictors of future depression are unlikely to be symptoms of incipient depression in most cases since the time span between the first examination and the onset of new major depression is too long to assume prodromal subclinical states of depressive episodes (mean 2.1 ± 0.9 years).

The multivariate logistic regression analysis to identify the most relevant preclinical markers of depression revealed that lack of joy and interest, poor concentration, increased appetite, lack of energy, joint pain and age contributed independently to the development of later depression (Table 3).

Dysphoria, insomnia, morning depth, feelings of inferiority, lack of self-confidence, indecisiveness, thinking about death and wish to die had no influence on the development of depression in a multivariate model, because they were associated with lack of joy and interest, poor concentration, appetite disturbance and lack of energy. The association was explained by correlations ranging from 0.105 to 0.404 (Cramer's index). The multivariate logistic regression analysis was necessary to prevent an influence of these associations on the results.

During follow-up, only two of the 51 subjects with a new depressive episode (3.9 %) developed a generalized anxiety disorder and two subjects (3.9 %) developed nicotine dependence in addition to their major depressive disorder.

Discussion

Lack of joy and interest, poor concentration, increased appetite, lack of energy and joint pain were the most relevant preclinical markers of late-onset depression (Table 3). In contrast, Berger et al. (1998) only found appetite disturbance and dysphoria as risk factors of late-onset depression. Their study is only in part comparable to our study, because current instead of lifetime symptoms were investigated. Our study indicates that there is a larger number of lifetime symptoms than current symptoms preceding late-onset depression. Consequently investigating lifetime symptoms is more comprehensive. Furthermore the mean age of the sample of Berger et al. (84.6 years) differs from the mean age of our sample (59.7 years) which corresponds better to the usual age at onset of late-onset depression.

In agreement with our univariate analyses Roberts et al. (2000) observed that symptoms like lack of joy and interest, feelings of inferiority, tiredness, dysphoria, thinking about death, insomnia, poor concentration and increased appetite were risk factors of future late-onset depression. In addition they observed that feelings of worthlessness, psychomotor disturbances and lack of appetite were also associated with depression. Differences concerning the number of symptoms may be explained by their focus on current symptoms and by not accounting for associations among different symptoms (no multivariate analysis was performed).

With respect to symptoms of somatic diseases, joint pain increased the risk of late-onset depression. Joint pain is typical of rheumatoid arthritis, which has been reported to be associated with major depression (Suarez-Mendoza et al. 1997). According to Gallagher et al. (1999) living with chronic pain leads to depression. In the present study, no relationship between abdominal, back or chest pain, headache, cardiopulmonary or gastrointestinal symptoms and depression could be observed, although chronic headache (Mitsikostas et al. 1999), myocardial infarction (Burg et al. 2001) and abdominal complaints (van Marwijk et al. 1996) were reported to be associated with depression.

A general problem in studies investigating the relationship between depression and somatic symptoms is to distinguish between patients becoming depressed because of a somatic disease and depressed subjects who tend to somatize. It was shown that somatization is a fre-

Table 3 Most relevant preclinical markers contributing in combination to the risk of late-onset depression identified by multivariate logistic regression analysis (N = 51)

	Odds Ratio	95 % CI	WALD X2, df, p
Lack of joy and interest	1.74	1.20–2.52	WALD $\chi^2 = 8.55$; df = 1; p = 0.003
Poor concentration	1.36	1.07–1.72	WALD $\chi^2 = 6.54$; df = 1; p = 0.011
More appetite	1.36	1.03–1.79	WALD $\chi^2 = 4.80$; df = 1; p = 0.028
Articulation pain	1.34	1.07–1.68	WALD $\chi^2 = 6.85$; df = 1; p = 0.009
Lack of energy	1.31	1.05–1.65	WALD $\chi^2 = 6.54$; df = 1; p = 0.019
Age	1.04	1.01–1.06	WALD $\chi^2 = 7.35$; df = 1; p = 0.007

quently occurring illness behavior of subjects suffering from depression (Kirmayer et al. 1996). Whether certain somatic diseases share a common pathophysiological basis with depression must be assessed in future studies.

In contrast to many studies showing female gender as a risk factor of depression (Coryell et al. 1992; van den Berg et al. 2000; Steffens et al. 2000), in the present study gender had no influence on the development of later depression. This may be explained by a selection bias associated with the method of recruitment (Heun et al. 1997), e. g., more men at risk for depression might have participated. However, the study revealed increasing age to be a risk factor of late-onset depression. Generally, the prevalence of depression decreases with increasing age with the lowest prevalence in people aged 65 and older (Wittchen et al. 1994), but no study focussing only on the relationship of age and the prevalence of depression in people aged 60 or older has been conducted yet.

We investigated a sample of elderly subjects. Early- and late-onset depression differ according to their symptomatology (Krishnan et al. 1995; Baldwin et al. 1995), e. g., early-onset depressed subjects suffer more often from lifetime symptoms of dysphoria, lack of joy and interest, tiredness, cognitive disturbances and feelings of worthlessness than late-onset depressed subjects (Heun et al. 2000). Thus, the results cannot be transferred to early-onset depression.

The results suggest that it is possible to evaluate the risk of depression by standard diagnostic instruments before the onset of the first episode of major depression. This is especially important for patients with late-onset depression as they are often not diagnosed with the consequence of under-treatment and increasing mortality (Gottfries, 2001). Further studies should focus on the age-effects of preclinical markers of depression.

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