INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY

Int J Geriatr Psychiatry 2006; **21**: 811–818.

Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1565

Predicting the onset of major depressive disorder and dysthymia in older adults with subthreshold depression: a community based study

Pim Cuijpers[1,2]*, Aartjan Beekman[2,3], Filip Smit[1,2] and Dorly Deeg[3]

[1]*Department of Clinical Psychology, Vrije Universiteit, Amsterdam, The Netherlands*
[2]*Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands*
[3]*Department of Psychiatry, Vrije Universiteit, Amsterdam, The Netherlands*

SUMMARY

Background It is well-established that the incidence of major depressive disorder is increased in subjects with subthreshold depression. A new research area focuses on the possibilities of preventing the onset of major depressive disorders in subjects with subthreshold depression. An important research question for this research area is which subjects with subthreshold depression will develop a full-blown depressive disorder and which will not.

Methods We selected 154 older subjects with subthreshold depression (CES-D > 16) but no DSM mood disorder from a longitudinal study among a large population based cohort aged between 55 and 85 years in The Netherlands. Of these subjects, 31 (20.1%) developed a mood disorder (major depression and/or dysthymia) at three-year or six-year follow-up. We examined risk factors and individual symptoms of mood disorder as predictors of onset of mood disorder.

Results Two variables were found to be significant predictors in both bivariate and multivariate analyses: eating problems and sleep problems. The incidence of mood disorders differed strongly for different subpopulations, varying from 9% (for those not having any of the two risk factors) to 57% (for those having both risk factors).

Conclusions It appears to be possible to predict to a certain degree whether a subject with subthreshold depression will develop a mood disorder during the following years. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — major depression; dysthymia; incidence; subthreshold depression; risk factors; prediction

INTRODUCTION

Although subthreshold depression has been defined in many different ways (Cuijpers and Smit, 2004), there is a growing body of research indicating that subthreshold depression is a highly prevalent condition (Horwarth *et al*., 1992; Cuijpers *et al*., 2004a) with a considerable impact on the quality of life of patients (Rapaport and Judd, 1998; Preisig *et al*., 2001) resulting in a strongly increased service utilization (Wagner *et al*., 2000), and it has been found to be associated with large-scale economic costs due to disability days (Broadhead *et al*., 1990).

Furthermore, the incidence of major depressive disorder is highly increased in subthreshold depression (Cuijpers and Smit, 2004), although this incidence rate depends strongly on the definition of subthreshold depression (Cuijpers and Smit, 2004). Because of this increased incidence, subjects with subthreshold depression have become the main target population of a new emerging area of research examining the possibilities of preventing the onset of new cases of major depressive disorder. Several recent studies in this area have found evidence that it is indeed possible to reduce the number of new cases of MDD by intervening in subjects with subthreshold depression (Clarke *et al*., 1995, 2001; Willemse *et al*., 2004; Cuijpers *et al*., 2005).

Subthreshold symptoms of depression may consist of three types of symptoms (Fava, 1999): prodromes, predicting the onset of an episode of major depression; residual symptomatology after recovery from an

*Correspondence to: Dr. P. Cuijpers, Professor of Clinical Psychology, Dept. of Psychology, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.
E-mail: P.Cuijpers@psy.vu.nl

Received 12 September 2005
Accepted 6 February 2006

earlier episode; or the depressive symptoms may constitute an independent condition, such as minor depression as defined in the DSM-IV, or recurrent brief depression, which are not definitely considered to be a diagnostic category.

One important research question for this area of prevention research is which subjects with subthreshold depression will develop a mood disorder and which will not. A more reliable assessment of the risk of developing a mood disorder in subjects with subthreshold depression will enable us to focus preventive interventions more on those with the highest risk. The few studies examining this subject have examined whether specific depressive symptoms predict the onset of major depression. These studies have found indications that subjects with feelings of guilt or worthlessness (Crum *et al*., 1994) and with concentration problems (Eaton *et al*., 1995) more often develop major depression than other subjects with subthreshold depression. There is also some evidence that the number of depressive symptoms is related to the onset of major depression (Crum *et al*., 1994). In a recent study, more general risk factors for getting major depression among subjects with subthreshold depression were examined, such as family history of depression, life events, personality characteristics, and chronic illness (Cuijpers *et al*., 2004b). It was found that family history and chronic physical illness best predicted the onset of major depression.

There are no studies in which both depressive symptoms and general risk factors are examined together to predict the onset of major depression in subjects with subthreshold depression. Furthermore, all earlier research in this area has focused on young and middle-aged adults, and no study has focused on older adults. In the current study, we will examine both depressive symptoms and general risk factors for developing major depression and dysthymia in older adults with subthreshold depression.

METHOD

Sampling, procedures and respondents

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing study on predictors and consequences of changes in well-being and autonomy in the population aged 55–85 years (Deeg *et al*., 1993). Sampling and procedures have been reported in detail elsewhere (Beekman *et al*., 1995, 2002). At baseline (1992/93), a large ($n = 3107$), age- and gender-stratified random sample of inhabitants, drawn from 11 community registries in three regions of the Netherlands, was interviewed. All interviews were conducted in the homes of respondents by trained and intensively supervised interviewers. Informed consent was obtained prior to the study, in accordance with legal requirements in the Netherlands.

The present study is based on a subsample which was created as follows. All subjects, minus 51 subjects who were lost due to item non-response, were screened for depression (scoring ≥ 16 on the Center for Epidemiological Studies—Depression scale, CES-D, see Measures). This resulted in a sample of 3056. Of these, 455 subjects were screen positives, and 326 of them were interviewed with the Diagnostic Interview Schedule (DIS, see Measures) to assess the presence of major depressive disorder and dysthymia. A similarly sized random sample of the screen negatives ($n = 320$) also received a diagnostic interview. The Diagnostic Interviews were administered by a different group of interviewers, who were blind to the CES-D scores. After three and six years after the baseline interview, the same subjects were re-interviewed with the DIS again.

For the present study, we examined subjects with subthreshold depression at the baseline interview, defined as scoring above the cut-off score of 16 on the CES-D (see below), but not currently having a major depression or dysthymia according to diagnostic criteria (assessed with the DIS, see below). We excluded subjects who had a major depressive disorder during the past six months. This resulted in a sample of 244 subjects. Next, we selected subjects for whom DIS data on the status of depressive disorder and dysthymia were available at one of the two follow-up interviews. This was the case for 154 of the 244 subjects.

We examined whether significant differences existed between the 154 participants and those who dropped out at the two follow-up measurements ($n = 90$). We compared the included subjects with the drop-outs on all variables described in Table 1. Three significant differences were found: more men (46%) than women (30.6%) dropped out ($p < 0.05$); more drop-outs occurred among those scoring positive on the DIS-item indicating ever having had no appetite (40.8%) than among those who did not (15.8%; $p < 0.01$); and there was more dropout among those who scored positive on the DIS-item indicating that they ever thought about death (44.1%) than among those who did not (31.7%; $p < 0.05$).

In the rest of this study, we used the group of 154 subjects with subthreshold depression at baseline. About two-thirds of the subjects were women (64.9%); 30.5% were aged 55–64, 27.4% 65–74, and 42.1% was 75+ years of age; 44.2% was

Table 1. Significant predictors of onset of mood disorder in subjects with subthreshold depression in bivariate and multivariate analyses ($n = 154$): Incidence Rate Ratios (IRR) and 95% confidence intervals[a]

	N (%)	Univariate analyses			Multivariate analyses[b]	Multivariate analyses[c]
		MDD	Dysthymia	MDD and/or dysthymia		
		IRR (95% CI)		IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Age (> 65 years)	105 (69.5)	8.58 (1.14 ~ 64.24)*		1.66 (1.08 ~ 8.87)*		
Low mastery	35 (23.7)			4.39 (1.04 ~ 18.47)*		
High urbanisation	62 (41.1)					
DIS-items on mood						
No appetite	32 (20.78)	4.08 (1.66 ~ 10.05)**	4.54 (1.46 ~ 14.07)**	3.74 (1.84 ~ 7.58)***	2.90 (1.32 ~ 6.40)**	3.24 (1.45 ~ 7.23)**
Ever ate too much	19 (12.3)		3.86 (1.16 ~ 12.83)*			
Sleep problems	88 (57.1)	3.04 (1.01 ~ 9.17)*		2.78 (1.20 ~ 6.46)*		2.60 (1.07 ~ 6.31)*
Tired	42 (27.3)			2.71 (1.34 ~ 5.48)**		
Restless	20 (13.0)	4.84 (1.90 ~ 12.28)**	8.29 (2.67 ~ 25.70)***	3.39 (1.56 ~ 7.37)**		
Feeling worthless	22 (14.3)	2.95 (1.12 ~ 7.75)*				
Slow thinking	11 (7.14)		4.72 (1.28 ~ 17.43)*	2.72 (1.05 ~ 7.09)*		

[a] not significant variables in any of the analyses were: gender, education (low/high), chronic illnesses, family history of depression, life time MDD, cognitive impairment, functional limitations, subjective health, and the DIS-items lost weight, ate too much, slept too long, slow, lack of interest, thinking of death, willing to die, suicide, suicide attempt.
[b] poisson regression analysis with the seven variables that were found to be significant ($p < 0.1$) in the univariate analyses, as predictors.
[c] poisson regression analysis with all variables as predictors.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

widowed; 40.9% was married; level of education was elementary in 53.2%; and 42.2% lived in a large city (Amsterdam).

Measures

The Center of Epidemiological Studies—Depression scale (CES-D) was used as a screener for depression, and as an indicator of the presence of subthreshold depression (that is, when scoring above the CES-D cut-off score, when no major depressive disorder or dysthymia were present according to the DIS). The CES-D (Radloff, 1977) is a 20-item scale, developed to measure depressive symptoms in the community. It has been widely used in older community samples and has good psychometric properties in this age group (Himmelfarb and Murrell, 1983; Radloff and Teri, 1986; Hertzog *et al*., 1990). The Dutch translation had similar psychometric properties in three previously studied samples of older adults in the Netherlands (Beekman *et al*., 1994). Due to the emphasis on affective items in the scale, the overlap with symptoms of physical illness is limited (Berkman *et al*., 1986). The CES-D generates a total score, ranging from 0 to 60. In order to identify respondents with clinically relevant levels of depression, the generally used cut-off score ≥ 16 was used. Using this score, the criterion validity of the CES-D for MDD was excellent (sensitivity 100%, specificity 88%; Beekman *et al*., 1997).

Diagnosis of MDD or dysthymia. In order to diagnose major depressive disorder and dysthymia, the Diagnostic Interview Schedule was used (DIS, Robins *et al*., 1991). We examined whether the included subjects met criteria for a mood disorder (MDD and/or dysthymia) at any time between baseline and follow-up measurements. The DIS was designed for epidemiological research and has been widely used among older adults. Interviewers were fully trained by certified staff, using the official Dutch translation of the DIS (Dingemans *et al*., 1985).

Predictors. As possible predictors of the incidence of a mood disorders we examined: (a) All indivual items of the DIS (MDD/dysthymia, life-time). These items indicate clinical features of the mood disorder. The items ask whether the subjects have ever met DIS criteria for the following symptoms: no appetite; lost weight; ate too much; sleep problems; slept too long; tired; slow; restless; had a lack of interest; felt worthless; had bad concentration; slow thinking; thought of death; willing to die; thought of suicide; had made a suicide attempt; (b) Demographic variables: female gender (1 = female, 0 = male); age over 65 years, which is the official retirement age in the Netherlands (1 = older than 65 years, 0 = younger); low education (dichotomized into 1 = elementary and high school, 0 = lower vocational and higher); living in an urban environment (1 = living in Amsterdam, 0 = living elsewhere).

Following the vulnerability–stress theory (Brown and Harris, 1978) and a recently published review on risk indicators of late-life depression (Cole and Dendukuri, 2003) the following predictors were also included: (c) Self-reported family history of depression (one question; yes/no); (d) Life time MDD (yes/no), as assessed with the DIS; (e) Cognitive impairment as measured with the Mini Mental State Examination (Folstein *et al*., 1975; 1 = MMSE < 24, 0 = MMSE 24–30); (f) Self-reported chronic illnesses (dichotomized, 1 = two or more, 0 = one or none) among them, diabetes mellitus, chronic obstructive lung disease, cardiac disease, arthritis of knee or hip, and cancer (Kriegsman *et al*., 1996).

Earlier studies have indicated that it is not so much the presence of chronic medical conditions that predict the onset of depression, but rather the functional limitations that may stem from them, the subjective appraisal of one's health, and finally the degree by which one's sense of mastery (locus of control) is affected (Ormel *et al*., 1997; Zarit *et al*., 1999; Geerlings *et al*., 2000; Smit *et al*., 2005). Therefore, the following measures were also included: (g) functional limitations (1 = one or more, 0 = none; Van Sonsbeek, 1988); (h) self-rated subjective health (1 = poor or sometimes good, sometimes bad, versus fair—very good, Central Bureau of Statistics, 1989); (i) low mastery (1 = score below the 50th percentile on the scale, 0 = above 50th percentile; Pearlin and Schooler, 1978).

All scales were either previously validated in comparable samples in the Netherlands, or in LASA pilot studies (Deeg *et al*., 1993).

Analyses

We examined the incidence at three- and at six-year follow-up. Because of the difference in follow-up length, we based our analyses on the incidence density rate, which indicates the number of incident cases per 100 person years, thus taking into account the variable exposure time.

First, we conducted a series of Poisson regression analyses, with the later onset of major depression or dysthymia (yes/no) as the dependent variable, and each of the demographic variables, the variables

selected on the basis of the vulnerability–stress theory, and the DIS-items as predictors. The predictors were entered into the Poisson regression model one at a time, thus producing bivariate incidence rate ratios (IRR). The IRR is the incidence rate of the exposed group relative to the unexposed group, while taking into account the unequal follow-up times as before, and can be interpreted as a relative risk. We conducted the same analyses with the onset of major depression only as the dependent variable, and once more with the onset of dysthymia only as the dependent variable.

Then, we conducted another Poisson regression analysis, with the onset of major depression and/or dysthymia (yes/no) as the dependent variable. But this time, we simultaneously entered all the variables that were found to be significant ($p < 0.05$) in the bivariate analyses, into the regression equation as predictors. In order to identify the most important predictors, we used the backwards removal of predictors from the regression equation. Next, we conducted a Poisson regression analysis with the onset of major depression or dysthymia (yes/no) as the dependent variable and all study variables together (demographic variables, the variables selected on the basis of the vulnerability–stress theory, and all DIS-items) as predictors. In this way we arrived at a parsimonious model in which only significant predictors were retained.

Finally, we explored what combinations of significant predictors of major depression yielded the best predictive power for the later onset of mood disorder. To this end, we made all possible combinations of the previously selected predictors (predictor 1: present or absent; predictor 2: present or absent; etcetera) and calculated for each combination the proportion of subjects that developed a mood disorder. This allowed us to examine whether specific combinations of risk factors can be used to predict mood disorders at individual case level.

RESULTS

Incidence

A total of 31 of the 154 subjects (20.1%) developed a mood disorder during the six-year follow-up (9 MDD only, 19 dysthymia only, and 3 both MDD and dysthymia).

Predictors of incidence

In the bivariate analyses in which the incidence of MDD and/or dysthymia was used as the dependent variable, seven variables at baseline were found to be significantly related to the onset of mood disorder at follow-up (Table 1): age (between 55 and 65, versus older; $p < 0.05$), low mastery ($p < 0.05$), and five DIS-items (ever no appetite, $p < 0.001$; ever sleep problems, $p < 0.05$; ever tired, $p < 0.01$; ever restless, $p < 0.01$; slow thinking, $p < 0.05$).

In the univariate analyses in which MDD only was used as the dependent variable, five variables were found to be significant predictors: old age, and four DIS-items (ever no appetite, sleep problems, restlessness, and feeling worthless), and with dysthymia as the dependent variable, four significant predictors were found (the DIS-items ever no appetite, ever ate too much, restlessness and slow thinking).

Because the number of subjects developing MDD or dysthymia was small, we combined the subjects who developed a mood disorder into one group. As indicated, we conducted a poisson regression analysis with the onset of mood disorder (yes/no) as the dependent variable and the seven variables that were found to be significantly related in the univariate analyses, as predictors (Table 1). Only one variable remained significant: ever no appetite ($p < 0.01$).

Then we entered all variables together as predictors in a poisson regression analysis, and found two variables to be significant: ever no appetite, $p < 0.01$, and sleep problems, $p < 0.05$).

Risk profiles and prognosis

We decided to examine two possible prognostic variables or risk indicators for developing mood disorder at follow-up that were found to be significant predictors in at least two of the three series of poisson regression analysis: problems with appetite, and sleep problems (both DIS items). We examined all possible combinations of these two predictors (present/absent), and examined for each combination or profile how many subjects developed a mood disorder and how many did not (Table 2). We also calculated the total number of risk factors and the number of subjects with 0, 1, or 2 risk factors that developed a mood disorder at follow-up.

For each profile, we calculated the incidence of mood disorder within that profile (Table 2), and the total percentage of the overall incidence that can be attributed to the subjects of this profile (the population attributable fraction, Table 2).

As can be seen from Table 2, the incidence of mood disorders differed strongly for different risk profiles. The incidence varied from 9% (for those not having any of the two risk factors) to 57% (for those having both risk factors). Because the number of subjects in

Table 2. Risk profiles for getting a mood disorder (MD) among subjects with subthreshold depression: (DIS) lack of appetite, and (DIS) sleep problems

Profile of risk factors		Having MD at follow-up (N)			Incidence within group	% of total Incidence[a]
Ever no appetite	Sleep problems	Yes	No	Total		
+	+	12	9	21	0.57	38.7
+	−	2	9	11	0.18	6.5
−	+	12	55	67	0.18	38.7
−	−	5	50	55	0.09	16.1
		31	123	154	0.20	100
Number of risk factors						
	0	5	50	55	0.09	16.1
	1	14	64	78	0.18	45.1
	2	12	9	21	0.57	38.7

[a] the population attributable fraction.

each of the profiles was very small, we did not conduct further analyses.

DISCUSSION

This study has several limitations. First, the number of subjects developing a mood disorder during follow-up was relatively small ($n = 31$). However, this small number could have easily resulted in no significant predictor of mood disorder. Therefore, the predictors we found to be significant can be considered to be very strongly related to the onset of mood disorder. Second, because of the small number of incident cases, we could not disthinguish between those subjects developing major depressive disorder and those who developed dysthymia. It is very well possible that the predictors of incidence differ for both disorders. This may also explain differences between the results of our study and comparable other studies. Third, we examined only a selection of relevant risk factors. For example, we did not examine hereditary predictor variables. Fourth, we found some significant differences between the subjects for whom follow-up data were available and drop-outs. This may have distorted the outcomes, especially as one of the significant predictors we identified was significantly different for drop-outs (the DIS-item 'ever having had no appetite'). Fifth, we only differentiated between three and six year follow-up, but did not exactly pinpoint the exact onset of MDD or dysthymia, which seems even more important for dysthymia which requires two years to meet criteria.

On the other hand, we did find indications as to which subjects with subthreshold depression will develop a mood disorder and which will not. First, some indications were found that low levels of mastery were related to the incidence of mood disorder. As far as we know, this is the first study in which mastery was examined as a predictor of mood disorder in subthreshold depression. This relation seems quite plausible, however, as low mastery in combination with depressive symptoms may be indicative of a lack of coping resources to resolve the depressive symptoms. On the other hand, in the multivariate analyses the results were not significant anymore, which may be related to the small number of subjects.

We did not find support for the relation between several other variables and onset of mood disorder that were found in other studies, such as a family history of mood disorder, and chronic physical illness (Cuijpers *et al*., 2004b). This may be related to the fact that we combined subjects with major depressive disorder and dysthymia, or to the fact that our study was conducted with older adults, while most other studies are conducted with younger adults.

Several DIS-items were found to be related to the onset of mood disorder in bivariate analyses, but most of them were no longer significant in the multivariate analyses. There was a strong relationship between eating problems (the DIS-item 'ever had no appetite') and onset of mood disorder, which remained significant in all multivariate analyses. It is hard to conceive why this specific item was such a strong predictor of mood disorder, while others were not. The same is true for sleep problems.

Sleep problems were also found to be a significant predictor of mood disorders. This is in agreement with an earlier population-based study, which also found that sleep problems were an important preditor of incidence of major depressive disorder, especially when the sleep problems persisted over some time (Ford and Kamerow, 1989). The relationship of sleep to subsequent health status was also confirmed by a more recent study (Dew *et al*., 2003), which showed

that sleep latencies of greater than 30 min predicted a two-fold elevation in mortality rates among healthy older adults over a 13-year follow-up.

Other DIS-items that have been found to be significantly related to the onset of mood disorder in subthreshold depression, such as concentration problems were not found to be significant predictors in our study. Again, this may be related to the fact that we combined subjects with major depressive disorder and dysthymia, or to the older adult population of our study. But it may also be related to the selective drop-out from our study.

We also examined if we could use the prognostic variables in predicting the onset of mood disorder in indivual subjects, by examining different profiles of these prognostic variables. Only few subjects without any of the two risk factors developed a mood disorder at follow-up (9%), and those having both risk factors had a very high chance of getting a mood disorder (57%). These results have to be considered very cautiously, because of the small number in each of the cells, and these data should only by seen as illustrations of what would be possible when larger numbers of subjects are be available. However, it does seem possible to identify quite well a considerable number of the subject who will develop a mood disorder. More research is clearly needed to develop instruments to identify subjects at high risk.

This study suggests, as earlier studies have, that it is possible to predict to a certain degree whether a subject will develop mood disorder when exposure to a small number of key variables is known. As the process of developing mood disorder depression is as yet poorly understood, replication in other samples and studies is important, which may allow greater power of analyses through meta-analysis of the results. More research can considerably enhance our understanding of that process.

KEY POINTS

- It is possible to predict to a certain degree whether a subject with subthreshold depression will develop a mood disorder during the following years.
- Life-time eating problems and sleep problems are significant predictors of the incidence of mood disorder in subjects with subthreshold depression.
- More than half of those having both risk factors (57%) develop a mood disorder.

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