

# Clinical cues for detection of people with undiscovered depression in primary health care: a case–control study

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**Aim:** To identify clinical cues indicative of depression in medical records of cases in primary care with undetected depression. **Background:** Depressive disorders are common; the lifetime risk for men and women is 27% and 45%, respectively. Despite effective treatment methods such as antidepressants and cognitive behavioural therapy, depression often remains undiscovered in primary care, with great implications both on the individual and societal level. **Methods:** Clinical cues indicating depression were sought in medical records the year before an opportunistic screening for depression in primary care. In a previous study of 221 patients in the waiting room of a primary care centre during 10 randomly selected days, 45 (20%) showed signs of depression (MADRS-S  $\geq$  12) and 60% of these were verified as having depressive disorders (Prime-MD). These 45 patients constitute the cases in the present study. Age- and gender-matched controls were selected among those who scored below the chosen cut-off level. **Findings:** Seventeen (38%) of the 45 cases compared with eight (18%) of the 45 controls had one or more cues [odds ratio (OR) 2.81; 95% confidence interval (CI): 1.06–7.43]. Sleep disturbance showed the greatest difference between cases and controls (OR 4.53; 95% CI: 1.17–17.55). A significant relationship was found between severity of depression, frequency of cues and lower functional level. Cues were twice as common in patients with undetected depression and their functional level was lower. A two-stage procedure, screening and a structured diagnostic interview, is recommended when sleep disturbances and lowered function are present.

**Key words:** cues depression; detection; primary care

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## Introduction

Depressive disorders are common; the point prevalence is 5% (Angst, 1992), and the lifetime risk for men and women is 27% and 45%, respectively (Rorsman *et al.*, 1990). Depression is

costly (Sobocki *et al.*, 2006) and leads to great suffering (Coulehan *et al.*, 1997). Most patients with depression can be effectively treated, and early detection should therefore be of great interest (Gelenberg and Hopkins, 2007).

The treatment prevalence among depressed individuals in the general population is low. In a survey of a defined geographic area (Jämtland County, Sweden) during 2001 and 2002, the point prevalence of depressed individuals was 4.5%, and 75% of them did not receive antidepressant

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medication (Henriksson *et al.*, 2006). It has been estimated that 12% of patients in primary care suffer from major depression (Salokangas *et al.*, 1996; Bodlund *et al.*, 1999). This figure is actually probably higher as depressed patients often remain undiscovered (Coulehan *et al.*, 1997; Lotfi *et al.*, 2010).

In a previous study of undetected depression in primary care, a two-step procedure was used with a screening [Montgomery Åsberg Depression Self Rating Scale (MADRS-S)] (Svanborg and Ekselius, 2003) of all patients in the waiting room and a subsequent diagnostic interview of patients above the cut-off level ( $\geq 12$ ). A majority of the latter were verified to have depression using the diagnostic manual Primary Care Evaluation of Mental Disorders (Prime-MD) (Spitzer *et al.*, 2000). It was concluded that 13% of all patients in the waiting room had an undetected depression (Lotfi *et al.*, 2010).

The reasons for not detecting depression have been addressed in several studies; there could be a lack of awareness of cues indicating depression or a lack of experience among healthcare professionals (Jameson and Blank, 2010). A lack of time and non-continuity in primary care may be other explanations. Updated knowledge seems to increase the rate of detection and treatment of depression, resulting in reduced suicide rates (Henriksson and Isacson, 2006; Szanto *et al.*, 2007). Thus, in order to increase the rate of detection, the primary care physician's awareness of cues indicating suspected cases should increase. Signs such as anxiety, irritability, disturbed sleep, increased guilt and decreased concentration and libido have been suggested in studies as symptoms or cues that precede depression, but no study has yet focused on cues in undetected cases of depression (Fava *et al.*, 1990; Lotfi *et al.*, 2010).

The aim of the present study was to find 'cues' for an early identification of patients with undetected depression in primary care.

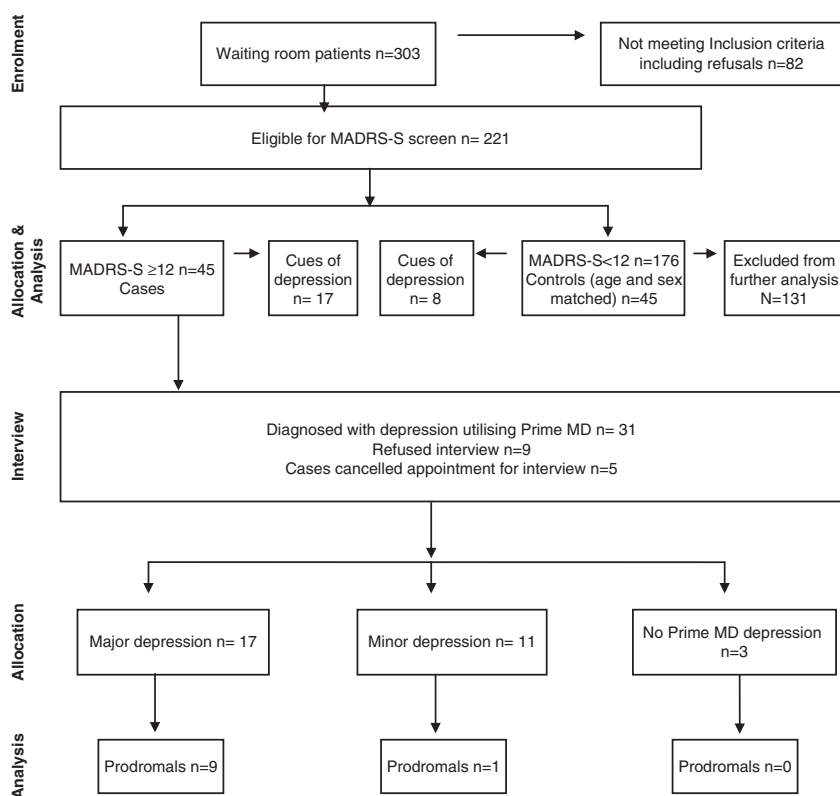
## Materials and methods

The study is based on a previous study on the occurrence and severity of undetected depression in primary care (Lotfi *et al.*, 2010). It was carried out in a primary care centre of a community in the north-eastern part of Stockholm with a fairly healthy,

well-educated and prosperous socio-demographic structure. The catchment area consisted of 9600 inhabitants with an even gender distribution and a predominant age range of 25–65 years (50%). As, in the previous study, it was found that 12% of the patients had undetected depression, the present study focused on possible cues noted in medical records during previous visits that differentiated patients with undetected depression from primary care patients without depression. In the previous study, after an informed consent, all consecutive patients aged  $\geq 18$  years in the waiting room at a primary care centre were screened for depression during a 10-day period in December 2004 with the MADRS-S (Svanborg and Asberg, 2001). The previous and present studies were approved by the Medical Ethics Committee in Stockholm, Sweden (Dnr 04-761/2).

The case recruitment flow is depicted in Figure 1. Those who were already being treated for depression or had another severe mental disorder (eg, severe suicidality, personality disorder) were not eligible; they either remained on their prescribed treatment or were transferred to specialised psychiatric care. Patients with MADRS-S scores  $\geq 12$  were identified as cases. Primary care patients in the waiting room the same day as the cases, and who scored below the cut-off level, were chosen as controls. Forty-five controls were selected from the 176 negative screens (MADRS-S  $< 12$ ), being the first age- and gender-matched patient who filled in the MADRS-S after an identified index case. A criterion for both cases and controls was having had one or more previous contacts with the primary care centre during the past year. Cases who agreed to be interviewed (31 of 45 with a MADRS-S score  $\geq 12$ ; 13% of all screened patients) were diagnosed using the Prime-MD (Spitzer *et al.*, 1994). The Prime-MD was performed within one week after the screening procedure. Seventeen (60.7%) and 11 (39.3%) of the cases were diagnosed with major (nine men and eight women) and minor (two men and nine women) depression, respectively (Lotfi *et al.*, 2010).

Primary care medical records for a period of one year preceding the screening and incident depression diagnoses were collected for the cases and the controls. One type of 'cue' was a sign indicating depression, defined as a note in the medical record made by the primary care physician that described at least *one* of the nine



**Figure 1** Case recruitment flow for patients with undetected depression. MADRS-S = Montgomery Åsberg Depression Self Rating Scale.

depressive criteria for major depressive episodes or associated features of depression, as defined in the DSM-IV-TR (American Psychiatric Association, 1994). Thus, the notes of the following symptoms were sought in medical records during the year preceding the index visit: Depressed mood; diminished interest or pleasure in all or almost all activities; body weight loss or gain or increase or decrease in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or inappropriate guilt; diminished concentration or indecisiveness; and recurrent thoughts of death or suicide. A number of physician-rated signs/symptoms were also noted such as tearfulness, irritability, brooding, obsessive rumination, anxiety phobias, excessive worrying over physical health and complaints of pain (eg, headaches or joint, abdominal, or other pains). If such notes were found for many visits, it was only recorded

once for the same patient. An experienced psychiatrist (S.H.) performed the assessments of depressive signs and cues. The identity and diagnosis of the patient was not known to the psychiatrist.

Another 'cue' was decreased functioning, defined by a low score on the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994). These notes were sought in the medical records of both cases and controls. To determine function, the GAF was applied by a trained psychiatrist (S.H.) to register symptoms and function descriptions that were found in the medical records on any or all of the occasions that the patient had visited the primary care centre. The symptom and function values (eg, impaired work and social functioning) were assessed separately, and the lowest value was chosen according to the manual for GAF assessments. In case of many GAF values from different visits, the highest value during the year studied was chosen. The rationale for

choosing the highest GAF value the previous year was to avoid false underestimations possibly related to the health care seeking situation.

### Statistics

The data were analysed using the SPSS 12.0.1 software for Windows. Descriptive statistics were used. The Mantel–Haenszel odds ratio was calculated to measure the association between the presence or absence of cues and the occurrence of a MADRS-S score  $\geq 12$ . The statistical tests used for comparisons were the  $\chi^2$ -test with Yates' correction for continuity or Fisher's exact test. Student's *t*-test was used for continuous variables.

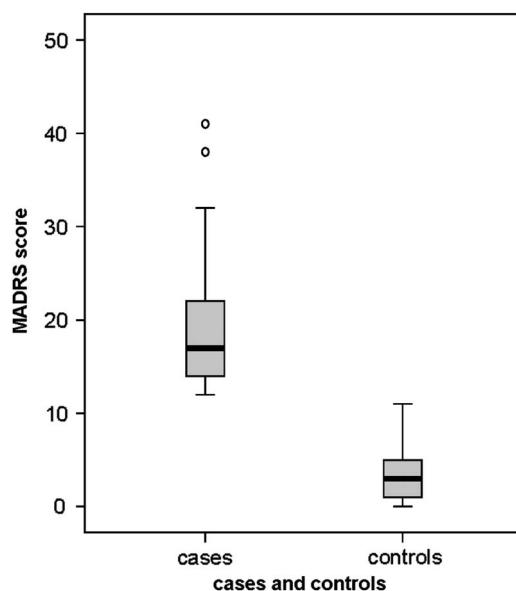
### Results

#### Cases and controls

Of a total of 221 individuals (median age of 58 and a range of 18–91 years), 45 patients scored  $\geq 12$  on the MADRS-S. Of these 45 patients (19 men and 26 women), the MADRS-S scores (mean  $\pm$  SD) for men and women were  $19.3 \pm 6.8$  and  $18.9 \pm 6.6$ , respectively (NS). Forty-five controls were selected from the 176 negative screens (MADRS-S  $< 12$ ). Thus, the first age- and gender-matched patient was chosen who filled in the MADRS-S after the index case and who had visited the primary care centre at least once during the previous year. MADRS scores for cases and controls are shown in Figure 2.

At least one depressive cue was found in 17 (38%) of the 45 cases compared with 8 (18%) of the 45 controls [odds ratio (OR) 2.81; 95% confidence interval (CI): 1.06–7.43]. The distribution of cues is shown in Table 1. In comparison, sleep disturbances were present in 11 (24%) of 45 cases and three (7%) of 45 controls (OR 4.53; 95% CI: 1.17–17.55). Other depressive symptoms were also numerically more common among cases, but the differences were not statistically significant. The GAF scores (mean  $\pm$  SD) for the cases and the controls were  $57 \pm 6.5$  and  $63 \pm 3.7$ , respectively ( $t = -2.6$ ,  $P < 0.05$ ).

According to Prime-MD, there were 28 verified cases with major and minor depression, and therefore we performed an odds ratio calculation between those among the 28 patients who had cues of depression ( $n = 10$ ) and the corresponding age- and gender-matched controls ( $n = 28$ ) who



**Figure 2** MADRS-S scores for cases with undetected depression ( $n = 45$ ; mean  $\pm$  SD;  $19.1 \pm 6$ ) and controls ( $n = 45$ ;  $3.5 \pm 3.2$ ) ( $P < 0.001$ ). MADRS-S = Montgomery Asberg Depression Self Rating Scale.

had cues of depression ( $n = 3$ ), and we still found a significant difference (OR 4.63; 95% CI: 1.11–19.26;  $P = 0.035$ ).

Cues indicating depression had been present in one of the 11 cases with a Prime-MD diagnosis of minor depression and in nine of the 17 with major depression (9% and 52.9%, Fisher's exact test, one-sided,  $P < 0.05$ ).

### Discussion

The main finding was that cues of depression found in medical records were twice as common in primary care patients who screened positive for depressive symptoms compared with those who screened negative. The single most important cue was sleep disturbances (insomnia or hypersomnia), a finding in accordance with that of other studies (Riemann and Voderholzer, 2003). Sleep disturbances have been suggested as a risk factor for depression in several studies (Dryman and Eaton, 1991; Breslau *et al.*, 1996). In a study of the course of remitted patients, self-reported sleep disturbance was found as a prodrome of relapse

**Table 1** Frequency of cues of depression in cases ( $n = 17$ ; MADRS-S  $\geq 12$ ) and controls ( $n = 8$ ; MADRS-S  $< 12$ ) in a consecutively recruited primary care sample ( $n = 221$ )

Symptoms	Cases ( $n = 17$ )		Controls ( $n = 8$ )	
	Men ( $n = 5$ )	Women ( $n = 12$ )	Men ( $n = 4$ )	Women ( $n = 4$ )
Depressed mood	4	5	1	3
Diminished interest or pleasure	0	3	1	1
Weight loss/gain	0	1	2	0
Sleep disturbances	3	7	1	2
Psychomotor agitation or retardation	1	3	0	0
Fatigue or loss of energy	5	6	2	2
Feelings of worthlessness or excessive or inappropriate guilt	0	4	1	1
Diminished ability to think or concentrate, or indecision	1	4	0	0
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	2	1	0	0
Tearfulness	0	3	0	2
Irritability	1	3	0	0
Brooding	0	1	1	1
Obsessive rumination	0	0	0	0
Anxiety phobias	2	6	3	1
Excessive worry over physical health	1	2	1	0
Complaints of pain (eg, headaches or joint, abdominal, or other pains)	2	5	2	2

MADRS-S = Montgomery Åsberg Depression Self Rating Scale.

(Perlis *et al.*, 1997). Ohayon even proposed that insomnia may be 'a ticking clock for depression' (Ohayon, 2007).

Patients with undetected depression had a lower functional status than those without. However, if a low level of functioning is present, it should be coupled with another cue to prevent over-diagnosing (Aragones *et al.*, 2006). The patient's level of functioning is an important health economic aspect of depression and should be followed up when evaluating the treatment result, as both discovery and improved function increase work productivity (Katzelnick *et al.*, 1997).

Other cues associated with depression were impaired work, loss of interest and fatigue. After the screening procedure, patients who were diagnosed with major depression had significantly more cues than patients with minor depression, suggesting that the presence of cues might qualify as a prognostic factor indicative of more severe pathology.

The primary care physicians did not act on cues they had noted in the medical records. They did not initiate any further investigation either by using screening or diagnostic interview methods, nor did they prescribe medication for any of the observed

symptoms, for example sleeping medication for a sleep disturbance.

Cues of depression, whether in the form of a single symptom, sub-threshold depression or a manifest depressive episode, were frequently missed by the primary care physicians in the present study. Non-recognition was not limited to patients with a relatively mild, brief depression but was also evident in patients with a persistent depression, a finding in line with that of others (Van Os *et al.*, 2006). This indicates that there is a lack of knowledge or incentive to look more closely into symptoms that may be relevant for health and ability to function in the general population.

Apart from being cues of depression in a primary care setting, one or more depressive symptoms might be seen as cues, residual symptoms or prodromes of relapse along a continuum in depressive disorders (Judd *et al.*, 1997). Fava and co-workers investigated such cues before the first onset of a major depressive disorder in psychiatric outpatients in comparison with controls (Fava *et al.*, 1990). Each of the patients reported at least one sub-syndromal cue before the onset of a depressive episode. Thus, one or more cues of

depressive symptoms may be regarded as risk factors for a later depressive episode both in recurrent and first episode depression.

### Limitations and strengths

The number of statistical analyses would normally require a correction for multiple analyses to avoid type 1 errors; however, we decided not to do it partly because of the limited number of cases and controls but also because our findings are consistent with other studies assuring their validity (Dryman and Eaton, 1991; Breslau *et al.*, 1996; Riemann and Voderholzer, 2003).

One of the strengths of this study is that the patients who were assessed for depressive symptoms were representative of the waiting room clientele, ranging in age from 18 to 91 years with a median age of 58, with 57.7% women. All the patients in the waiting room were invited to go through the screening procedure. Cases and controls were found in the same way. As the frequency of cues in the cases was compared with that in controls matched for sex and age, these potential confounders were controlled for. Furthermore, the assessment of the cues in the medical records was done by an independent investigator who was blinded to the screening results.

A weakness of the study was that the cues were identified in retrospect from notes made by the primary care physicians. The notes were regular notes in the medical record that were not recorded in a systematic manner. A prospective approach using a structured interview or screening method might have reduced the risk for bias. Nonetheless, by using regular 'real-life' medical records, it was revealed that the primary care physicians were aware of the symptoms but did not proceed with further actions. Another weakness is that the study was performed in one single site limiting the generalisability of the results. The findings are, however, consistent with those from other studies confirming their credibility (Fava *et al.*, 1990).

These findings, together with those in our previous study in the same patients, suggest that when certain cues (eg, sleep disturbances, decreased functioning and at least one sign of depression) are present, a subsequent two-stage opportunistic screening procedure may reveal both minor and major depressive episodes that otherwise would have been undetected (Lotfi *et al.*, 2010). In such

cases, anti-depressive medication and cognitive behavioural therapy, combined or given separately, could be initiated to prevent prolonged functional disability and health problems (Kupfer *et al.*, 1989).

### Conclusion

On the basis of the these findings, when cues of depression, especially sleep disturbances and decreased functioning, are present, implementation of a two-stage diagnostic procedure is suggested to improve the overall health situation in a primary care clientele. Suggestions for future research include studying the health economic consequences in order to find both overall health-related incentives and financial incentives for such strategies. Furthermore, qualitative research, for example interview studies with GPs, may clarify the underlying reasons why depression remains undetected despite cues.

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### Declaration of interest

The authors report no conflicts of interest. The authors are responsible for the design, content and writing of the article.

### References

- American Psychiatric Association. 1994: *Diagnostic and statistical manual of mental disorders DSM-IV-TR*, fourth edition. Washington, DC: American Psychiatric Association.
- Angst, J. 1992: Epidemiology of depression. *Psychopharmacology (Berl)* 106, Suppl, S71–74.



- Aragones, E., Pinol, J.L. and Labad, A.** 2006: The overdiagnosis of depression in non-depressed patients in primary care. *Family Practice* 23, 363–68.
- Bodlund, O., Andersson, S.O. and Mallon, L.** 1999: Effects of consulting psychiatrist in primary care. 1-year follow-up of diagnosing and treating anxiety and depression. *Scandinavian Journal of Primary Health Care* 17, 153–57.
- Breslau, N., Roth, T., Rosenthal, L. and Andreski, P.** 1996: Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biological Psychiatry* 39, 411–18.
- Coulehan, J.L., Schulberg, H.C., Block, M.R., Madonia, M.J. and Rodriguez, E.** 1997: Treating depressed primary care patients improves their physical, mental, and social functioning. *Archives of Internal Medicine* 157, 1113–20.
- Dryman, A. and Eaton, W.W.** 1991: Affective symptoms associated with the onset of major depression in the community: findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. *Acta Psychiatrica Scandinavica* 84, 1–5.
- Fava, G.A., Grandi, S., Canestrari, R. and Molnar, G.** 1990: Prodromal symptoms in primary major depressive disorder. *Journal of Affective Disorders* 19, 149–52.
- Gelenberg, A.J. and Hopkins, H.S.** 2007: Assessing and treating depression in primary care medicine. *American Journal of Medicine* 120, 105–08.
- Henriksson, S., Asplund, R., Boethius, G., Hallstrom, T. and Isacson, G.** 2006: Infrequent use of antidepressants in depressed individuals (an interview and prescription database study in a defined Swedish population 2001–2002). *European Psychiatry* 21, 355–60.
- Henriksson, S. and Isacson, G.** 2006: Increased antidepressant use and fewer suicides in Jamtland county, Sweden, after a primary care educational programme on the treatment of depression. *Acta Psychiatrica Scandinavica* 114, 159–67.
- Jameson, J.P. and Blank, M.B.** 2010: Diagnosis and treatment of depression and anxiety in rural and nonrural primary care: national survey results. *Psychiatric Services* 61, 624–27.
- Judd, L.L., Akiskal, H.S. and Paulus, M.P.** 1997: The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *Journal of Affective Disorders* 45, 5–17, discussion 17–8.
- Katzelnick, D.J., Kobak, K.A., Greist, J.H., Jefferson, J.W. and Henk, H.J.** 1997: Effect of primary care treatment of depression on service use by patients with high medical expenditures. *Psychiatric Services* 48, 59–64.
- Kupfer, D.J., Frank, E. and Perel, J.M.** 1989: The advantage of early treatment intervention in recurrent depression. *Archives of General Psychiatry* 46, 771–75.
- Lofth, L., Flyckt, L., Krakau, I., Martensson, B. and Nilsson, G.H.** 2010: Undetected depression in primary healthcare: occurrence, severity and co-morbidity in a two-stage procedure of opportunistic screening. *Nordic Journal of Psychiatry* 64, 421–27.
- Ohayon, M.M.** 2007: Insomnia: a ticking clock for depression? *Journal of Psychiatric Research* 41, 893–94.
- Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X. and Kupfer, D.J.** 1997: Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *Journal of Affective Disorders* 42, 209–12.
- Riemann, D. and Voderholzer, U.** 2003: Primary insomnia: a risk factor to develop depression? *Journal of Affective Disorders* 76, 255–59.
- Rorsman, B., Grasbeck, A., Hagnell, O., Lanke, J., Ohman, R., Ojesjo, L. and Otterbeck, L.** 1990: A prospective study of first-incidence depression. The Lundby study, 1957–72. *British Journal of Psychiatry* 156, 336–42.
- Salokangas, R.K., Poutanen, O., Kaartinen-Paschalis, M. and Stengard, E.** 1996: Detection, diagnosis and treatment of depression by primary care physicians. *Duodecima* 112, 265–71.
- Sobocki, P., Jonsson, B., Angst, J. and Rehnberg, C.** 2006: Cost of depression in Europe. *Journal of Mental Health Policy Economics* 9, 87–98.
- Spitzer, R.L., Williams, J.B., Kroenke, K., Hornyak, R. and McMurray, J.** 2000: Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *American Journal of Obstetrics and Gynecology* 183, 759–69.
- Spitzer, R.L., Williams, J.B., Kroenke, K., Linzer, M., Degruy, F.V. III, Hahn, S.R., Brody, D. and Johnson, J.G.** 1994: Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *The Journal of the American Medical Association* 272, 1749–56.
- Svanborg, P. and Asberg, M.** 2001: A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *Journal of Affective Disorders* 64, 203–16.
- Svanborg, P. and Ekselius, L.** 2003: Self-assessment of DSM-IV criteria for major depression in psychiatric out- and inpatients. *Nordic Journal of Psychiatry* 57, 291–96.
- Szanto, K., Mulsant, B.H., Houck, P.R., Dew, M.A., Dombrowski, A., Pollock, B.G. and Reynolds, C.F. III** 2007: Emergence, persistence, and resolution of suicidal ideation during treatment of depression in old age. *Journal of Affective Disorders* 98, 153–61.
- Van Os, T.W., Van Den Brink, R.H., Van Der Meer, K. and Ormel, J.** 2006: The care provided by general practitioners for persistent depression. *European Psychiatry* 21, 87–92.