The interplay between depression, anxiety and physical health

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Chapter 6

The impact of chronic somatic diseases on the course of depressive and anxiety disorders

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ABSTRACT

Background

In clinical practice chronic somatic diseases are often co-morbid to psychiatric disorders. Little is known about their impact on psychiatric disorders, particularly on prognosis. The objective of this study was to determine the impact of chronic somatic diseases on the 2-year course of depressive and anxiety disorders.

Methods

Data from the Netherlands Study of Depression and Anxiety (NESDA) were used. Participants (n=1,209) with a depressive and/or anxiety disorder and with or without somatic diseases at baseline were followed up for two years. Somatic diseases were based on self-report and subsequently confirmed with medication use. Course of depressive and anxiety disorders was assessed by the CIDI psychiatric interview and Life Chart Interview. Descriptive statistics, binary and multinomial logistic regression analyses were used.

Results

The presence of musculoskeletal disease (OR=1.97; 95% CI=1.29-3.01) was associated with a higher risk of having a depressive and/or anxiety disorder after two years. Diabetes (OR=2.77; 95% CI=1.15-6.66) increased the risk for a recurrent or chronic course of depression and anxiety. A stricter definition of self-reported somatic disease, with medication confirmation, did not change associations. None of the other somatic diseases (e.g. respiratory or digestive disease or cancer) nor the number of somatic diseases or number of medications used impacted on the depression or anxiety course.

Conclusions

Depressed and/or anxious patients have a more unfavorable course when they also have musculoskeletal disease or diabetes.

INTRODUCTION

In recent years, researchers have put a great effort in recognizing predictive factors for the variability in the course of depressive and anxiety disorders. Chronic somatic disease has been recognized as an important risk factor for the occurrence of depressive and anxiety disorders[1-5], but may also be a vulnerability factor for the persistence of depression and anxiety. Several mechanisms for the negative impact of somatic disease on prognosis have been suggested. For instance, somatic diseases may have a negative influence on the recognition of mental health problems[6], receipt of and response to adequate treatment[7;8], but may also directly negatively impact on the overall well-being and functioning of depressed or anxious patients[9-12]. In addition, biological mechanisms of underlying somatic diseases (e.g. metabolic abnormalities or inflammation) have also been associated with poorer prognosis of depressive and anxiety symptoms[13;14]. There is evidence for the longitudinal association between somatic disease and a poorer course of depressive[2;15-21] and anxiety[16] disorders. Few studies, however, have investigated the relationship between specific somatic diseases and course of depression and anxiety longitudinally. Wells et al[22] found that a lifetime history of myocardial infarction was associated with persistent depression, whereas hypertension and insulin-dependent diabetes were not. Hypertension, arthritis, cardiovascular disease and peptic ulcer were associated with persistence of symptoms of depressive and anxiety disorders in a study with one year follow-up whereas COPD, asthma and diabetes were not[16]. The above mentioned studies concerning the impact of specific somatic diseases on the course of depressive and anxiety disorders differ in populations, settings and methodology used[23]. Overall, there is a lack of sufficient and reliable data on the role (specific) somatic diseases play in the course of depressive and even more in the course of anxiety disorders[24]. This study therefore examined their influence on the 2-year course of depressive and anxiety disorders.

METHOD

Sample

The Netherlands Study of Depression and Anxiety (NESDA) is an eight-year ongoing cohort study consisting of 2,981 participants (18-65 years old), recruited from community, general practice and secondary mental health care. Participants with anxiety and/or depressive disorders (78%) and mentally healthy controls (22%), are being monitored to investigate the long-term course and consequences of depressive and anxiety disorders. Penninx et al[25] provided a detailed description of the NESDA study design and sampling procedures.

During the baseline interview the participants were screened for a depressive and/or anxiety disorder using the DSM-IV based[26] Composite International Diagnostic Interview (CIDI, version 2.1)[27;28]. The sample was then restricted to 1,456 subjects with a 6-month depressive or anxiety diagnosis, who confirmed symptoms in the month prior to baseline at either the CIDI recency

questions or the Life Chart Interview (LCI)[29]. Of the eligible participants, 1,209 (83.0%) participated in the two-year follow-up interview and were included in the current study. Non-response was significantly higher among those with younger age, lower education, non-North European ancestry and depressive disorder, but was not associated with gender or anxiety disorder as confirmed in the overall NESDA sample[30].

Measurements

We used different sources to assess chronic somatic disease status, namely self-report as well as medication use information:

Self-reported chronic somatic diseases and disease categories

Kriegsman[31] showed that participants' self-reports of somatic diseases were reliable when compared to information obtained from their general practitioners. NESDA therefore included a face-to-face interview instrument about common somatic diseases. First, participants were asked whether they are diagnosed with any of the mentioned specific somatic diseases. To assess diseases most 'objectively', somatic disease was only considered in the analyses if it is treated by a healthcare professional or when medication is being used. Next, we classified the somatic diseases into disease categories: cardiometabolic, respiratory, digestive, neurological, musculoskeletal, endocrine and cancer (Table1). For cancer not only current treatment but also reported previous radiation, chemotherapy or operation in the past was taken into account. For specific somatic diseases with a sample size of at least 30 persons, we conducted additional analyses to see whether the specific diseases within the disease categories differed in their impact on the course of depression and anxiety.

Chronic somatic disease after medication-confirmation

In order to define somatic diseases more strictly, medication use was clustered for specific somatic diseases and disease categories. Participants were requested to bring their medication containers of medications used in the past month to the baseline interview. All somatic medications were registered per person, and classified according to the World Health Organization Anatomical Therapeutic Chemical coding [ATC coding][32]. Self-reported somatic disease was confirmed with the appropriate registered somatic medication[32] following the definitions listed in Table 1. Medication use was only considered present when taken regularly, at least 50% of the time, except for, the "when necessary" preparations; nitrate vasodilators and anti-migraine medication, which were included if used when necessary or more often, and immunosuppressants, which were also included when used less than 50% of time, because patients often use these latter medications on a weekly basis. Acetylsalicylic acid was registered for cardiometabolic diseases as anti-clotting medicine when lower or equal to 100 mg, and registered as painkiller for dosages over 100 mg.

In addition to disease specific indicators, we also created general indicators of overall disease burden: the number of self-reported somatic disease categories per patient, and the number of used medications per patient.

Course of depressive and anxiety disorder

After two years, a follow-up assessment was conducted. We used two outcome measures to assess the course of depressive and anxiety disorders. Our first outcome measure was psychiatric status after two years based on the presence of CIDI DSM-IV diagnosed depressive or anxiety disorder (6-month recency).

Besides psychiatric status after two years, we defined the clinical course trajectory of the index disorder. This was based on the LCI, completed for all persons with detected symptoms at the 2-year CIDI interview. In the LCI a calendar method is used; life events in the past two years were recalled to refresh memory, after which the presence of depressive and anxiety symptoms was determined separately for each month. In addition, for each month with reported symptoms, severity was assessed. Symptoms on LCI were only considered to be present when at least of mild severity. The clinical course trajectories included three categories on the basis of both their depressive and anxiety symptoms over time: a) early sustained remission, within six months without recurrence of any symptoms during follow-up, b) late sustained remission, remission after six months without recurrence, c) remission with recurrence of depressive or anxiety symptoms later on or chronic course, with at least mild symptoms during the entire follow-up period. Remission of the index disorder was defined based on LCI as the occurrence of no symptoms for three consecutive months[33].

Covariates

Sociodemographic covariates included age, sex and years of education[16;34;35].

Statistical analysis

Descriptive statistics were used to describe somatic disease indicators and sample characteristics. With logistic regression analyses we assessed the association between somatic disease variables with depressive and anxiety disorders at two year follow-up, after adjustment for covariates. We additionally conducted similar analyses for specific somatic diseases. Then, we repeated the analyses for the medication-confirmed somatic diseases and disease categories. Subsequently, after adjusting for the basic covariates, we used multinomial regression analyses to assess the associations of self-reported somatic disease indicators and clinical course trajectories with early sustained remission as reference category.

RESULTS

Table 1 describes the chronic somatic disease categories, constructed from self-report and from self-report with medication confirmation[32]. Cardiometabolic diseases were most frequently reported (17.6%), after medication confirmation this only dropped slightly to 15.6%. The number of patients with musculoskeletal disease and the number of patients with cancer declined more strongly.

The mean age of the 1,209 respondents was 42.1 years and 66% was female (Table 2). 56.7% reported no chronic somatic disease, 27.6% had one, and 15.7% had two or more somatic diseases. The average number of medications used was 2.3 (SD 2.2). 61.5% of the sample still had a disorder after two years and 62% had a recurrent or chronic course during the two years of follow up.

In Table 3 odds ratios (OR), 95% confidence intervals and p-values are shown. Only musculoskeletal disease category was significantly associated with still having a depressive and/or anxiety disorder at 2-year follow-up (OR=1.97; 95% CI=1.29-3.01). No associations were found for respiratory, digestive, endocrine diseases or cancer, the number of diseases and the number of medications used. The association with musculoskeletal disease remained strong after medication-confirmation (OR=1.65; 95% CI=0.86-3.16) but lost its significance.

Table 1: Classification of chronic somatic diseases.

Chronic somatic disease categories	N, %	Self-report	N, %	Medication-confirmation ([ATC coding])	Remaining (%)
Cardiometabolic	213 (17.6)	Hypertension, angina pectoris, history of cardiac disease (myocardial infarction or cardiac arrhythmia, heart failure, status after heart surgery), CVA, diabetes	188 (15.6)	antihypertensives [C02], diuretics [C03], beta blocking agents [C07], calcium channel blockers [C08], agents acting on renin-angiotensin system [C09], lipid modifying agents [C10], nitrate vasodilators [C01DA] or anticoagulant/ antiplatelet agents [B01, N02BA01<=100mg, N02BA15], medication used in diabetes [A10]	88.3
Respiratory	123 (10.2)	Asthma, chronic bronchitis, pulmonary emphysema	66 (5.5)	nasal preparations [R01], medication for obstructive airway diseases [R03], cough and cold preparations [R05], antihistamines for systemic use [R06], other respiratory system products [R07], corticosteroids for systemic use [H02]	53.7
Musculoskeletal	131 (10.8)	Osteoarthritis, rheumatoid arthritis, fibromyalgia, systemic lupus erythematodes	50 (4.1)	anti-inflammatory and anti-rheumatic products [M01], opioids [N02A], other analgesics and antipyretics [N02B], corticosteroids for systemic use [H02], immunosuppressants [L04]	38.2
Digestive	153 (12.7)	Ulcer (stomach or intestinal), irritable bowel syndrome, Crohn's disease, colitis ulcerosa, diverticulitis, liver cirrhosis, hepatitis, constipation	85 (7.0)	medication for acid related disorders [A02], medication for functional gastrointestinal disorders [A03], antiemetics and antinauseants [A04], bile and liver therapy [A05], laxatives [A06], antidiarrheals-intestinal anti-inflammatory/anti-infective agents [A07], corticosteroids for systemic use [H02], immunosuppressants [L04]	55.6
Neurological	42 (3.5)	Migraine, epilepsy, multiple sclerosis, peripheral neuropathy, hernia	19 (1.6)	analgesics [N02], non-steroidal anti-inflammatory and anti-rheumatic products [M01A], anti-inflammatory/anti-rheumatic agents in combination [M01B], antiepileptics [N03], corticosteroids for systemic use [H02], interferon [L03AB02]	45.2
Endocrine	39 (3.2)	Thyroid dysfunction	29 (2.4)	medication used in thyroid dysfunction [H03]	74.4
Cancer	80 (6.6)	Throat, thyroid, lung, esophagus, bowel, stomach, liver, uterus, cervix, ovary, bladder, testicle, prostate, skin, brain, blood, lymphnodes	18 (1.5)	medication used in cancer treatment [L01,L02,L03,L04] analgesic medication (opioids [N02A], other analgesics and antipyretics [N02B] and non-steroidal anti-inflammatory and anti-rheumatic products [M01A], anti-inflammatory/ anti-rheumatic agents in combination [M01B]	22.5

Table 2: Baseline Sample Characteristics.

Characteristics	Population (n=1,209)
Sample characteristics	
Female gender, %	66.0
Age in years, Mean (SD)	42.1 (12.3)
Education in years, Mean (SD)	11.8 (3.3)
Baseline clinical characteristics	
Depressive disorder, %	22.1
Anxiety disorder, %	40.3
Co-morbid disorder, %	37.6
Chronic somatic disease characteristics	
Number of diseases, Mean (SD)	0.7 (0.9)
0, %	685 (56.7)
1, %	334 (27.6)
>1, %	190 (15.7)
Number of medications, Mean (SD)	2.3 (2.2)
Outcome characteristics	
Psychiatric disorder after two years, %	61.5
Clinical course trajectory, %	
Early recovery (<6 months)	24.6
Late recovery (>= 6 months)	13.4
Recurrent and chronic course	62.0

Table 3: Associations between baseline somatic disease and medication use and a depressive and/or anxiety disorder at 2-year follow up [a].

Baseline variable	Self-report		Medication-confirmation	
	OR (95% CI)	p [b]	OR (95% CI)	p [b]
Chronic somatic disease categories				
Cardiometabolic	1.20 (0.86-1.69)	.286	1.30 (0.91-1.86)	.154
Respiratory	0.86 (0.58-1.26)	.430	0.89 (0.53-1.49)	.663
Musculoskeletal	1.97 (1.29-3.01)	.002	1.65 (0.86-3.16)	.134
Digestive	1.02 (0.72-1.46)	.898	1.01 (0.63-1.61)	.967
Neurological	0.60 (0.33-1.12)	.110	0.53 (0.21-1.32)	.050
Endocrine	0.84 (0.43-1.61)	.593	1.12 (0.51-2.44)	.780
Cancer	1.18 (0.73-1.91)	509	1.43 (0.50-4.08)	.499
Number of diseases				
continuum	1.08 (0.94-1.25)	.178	1.09 (0.92-1.29)	.322
0	1.00 [c]		1.00 [c]	
1	1.29 (0.97-1.70)	.078	1.30 (0.97-1.74)	.080
>1	1.14 (0.80-1.62)	.477	1.09 (0.72-1.66)	.678
Number of medications				
continuum	1.03 (0.97-1.09)	.358	n.a.	

a Adjusted for age, sex and years of education

b Using logistic regression analyses

c Reference category

n.a. not applicable

Table 4 shows results for the specific somatic diseases within categories that affected at least 30 persons. Only osteoarthritis showed a significant association with a mental disorder at 2-year follow-up. Diabetes showed the strongest associations from the cardiometabolic category, however, non-significant (without medication-confirmation: OR=1.51; 95% CI=0.84-2.86, and with: OR=1.81; 95% CI=0.87-3.76). Tables 3 and 4 show that the associations of self-reported somatic diseases with a depressive or anxiety disorder after 2 years hardly differed from the stricter medication-confirmed somatic diseases.

Table 5 displays the association between somatic disease categories and clinical course trajectories over two years. The results of multinomial logistic regression analyses showed that the cardiometabolic disease category was associated with having a recurrent or chronic course (OR=1.54; 95% CI=1.02-2.31). After conducting the same analyses for specific somatic diseases this association was shown to be mainly driven by diabetes (OR=2.77; 95% CI=1.15-6.66) and not by hypertension (OR=1.26; 95% CI=0.80-2.00) or cardiac disease (OR=1.21; 95% CI=0.64-2.30; data not shown in Tables). The number of somatic diseases and number of medications were not significantly associated with clinical course trajectories.

Table 4: Association between baseline specific somatic diseases and the presence of a depressive and/or anxiety disorder at 2-year follow up [a].

Baseline variable	Self-report			Medication-confirmation		
	N	OR (95% CI)	p [b]	N	OR (95% CI)	p [b]
Cardiometabolic						
Hypertension	145	1.13 (0.77-1.67)	.528	140	1.15 (0.77-1.70)	.495
History of cardiac disease	64	0.88 (0.52-1.50)	.646	51	0.86 (0.48-1.56)	.626
Diabetes	55	1.55 (0.84-2.86)	.165	41	1.81 (0.87-3.76)	.112
Respiratory						
Asthma	71	0.73 (0.45-1.19)	.209	41	0.62 (0.33-1.16)	.135
Chronic bronchitis and pulmonary emphysema	52	1.05 (0.78-1.41)	.765	25	1.80 (0.71-4.57)	.217
Musculoskeletal						
Osteoarthritis	98	1.69 (1.05-2.71)	.031	36	1.70 (0.78-3.68)	.180
Digestive						
Ulcer	45	0.96 (0.52-1.79)	.902	29	0.94 (0.43-2.01)	.864
IBS	44	0.67 (0.37-1.24)	.202	23	0.64 (0.28-1.46)	.288

a Basic adjustments: for age, sex and years of education

b Using logistic regression analyses

Table 5: Multinomial model for self-reported somatic disease and the clinical course trajectories of depressive and/or anxiety disorders with early recovery as reference outcome [a].

Baseline variable	Late recovery		Recurrent or chronic course	
	OR (95% CI)	p [b]	OR (95% CI)	p [b]
Chronic somatic disease categories				
Cardiometabolic	1.38 (0.78-2.43)	.272	1.54 (1.02-2.31)	.038
Respiratory	1.23 (0.66-2.29)	.507	0.99 (0.63-1.56)	.958
Musculoskeletal	1.20 (0.61-2.35)	.598	1.45 (0.90-2.33)	.125
Digestive	0.88 (0.49-1.59)	.681	0.95 (0.64-1.42)	.811
Neurological	1.31 (0.55-3.15)	.545	0.61 (0.30-1.25)	.175
Endocrine	2.21 (0.83-5.93)	.113	1.08 (0.47-2.47)	.860
Cancer	1.69 (0.80-3.60)	.170	1.18 (0.66-2.13)	.578
Number of diseases				
Continuum	1.22 (0.97-1.54)	.095	1.12 (0.94-1.32)	.206
Number of medications				
Continuum	1.01 (0.92-1.11)	.873	1.03 (0.96-1.10)	.445

a Adjusted for age, sex and years of education
b Using multinomial regression analyses

DISCUSSION

Our study, within a large cohort of depressed and anxious participants, shows that especially musculoskeletal disease and diabetes are associated with a poorer course of depressive and anxiety disorders. No other chronic somatic disease, nor their number, nor the number of medications used impacted significantly on the course of depression and anxiety.

Few studies have examined the link between specific somatic diseases and the course of depressive and/or anxiety disorders. Most of these studies used a single measure of somatic disease rather than determining the impact of specific somatic diseases. Moreover, although studies on the occurrence of psychiatric disorders have been conducted in particular chronic somatically ill patients, the somatically ill patients with psychopathology have been rarely studied over time.

The observation that musculoskeletal disease, in particular arthritis, is significantly associated with having a depression and/or anxiety at 2-year follow-up agrees with results found by Kisely et al[16]. Arthritis (osteoarthritis and rheumatoid arthritis) is generally characterized by a slowly progressive decline in physical and social role functioning and lifestyle adjustments, as a consequence of pain of the joints and disability[36;37]. The pain and disability may be worse than for other diseases, which might explain why depressive and anxiety symptoms occur and may more often persist over time[38;39]. In our study, after medication confirmation of musculoskeletal disease the associations with course of depression and anxiety were still strong, however no longer statistically significant. The number of patients with musculoskeletal disease declined strongly after medication confirmation. This is clinically understandable as it filters out patients who use specific rheumatoid medication and/or use pain medication at least 50% of time. However, many persons are reluctant to use analgesic medication on a continuous basis, because of fear for addiction or other negative effects.

In our study, diabetes made patients more prone towards a recurrent or chronic course of depressive and/or anxiety disorders. Interestingly, Wells et al. and Kisely et al.[16;22] did not find an association between diabetes and course in a depressed and anxious population. However, their studies only assessed current depression and anxiety at a few waves, which may not pick up on a fluctuating recurrent course as was assessed with the Life Chart Interview in our study. Depression and anxiety have shown to be associated with hypothalamic-pituitary-adrenocortical axis abnormalities, alterations in the autonomous nervous system and metabolic dysregulations[40-44], which could all contribute to poorer glycemic control and more diabetes symptoms[42;45;46]. In patients with both depression and/or anxiety and diabetes, physical inactivity, poor self-care, poor adherence to medical treatment, poorer glycaemic control and more diabetes symptoms have been found[47-51]. Consequently, less well-controlled diabetes might lead to neurochemical changes that result in worse depression and anxiety over time[46;52]. This may be an innovative perspective for future research.

Our study has some important strengths. We investigated a large sample of participants with a depressive or anxiety disorder over a period of two years. We undertook this study among participants from the general population, general practice and secondary mental health care settings whereas many studies used participants from one specific setting only[16;19;21]. Furthermore, we were able to assess somatic disease by self-report and more objectively by additionally considering medication use, which might be a more reliable and accurate outcome than self-report only. Compared to prior studies, we had a considerably higher number of depressed and anxious patients, whom all fulfilled psychiatric DSM-IV-criteria at baseline. Our study also has some limitations. The presence of somatic disease was not assessed in medical records. However, self-report on somatic disease has shown good concordance with medical records in previous research[31]. Moreover, somatic diseases with confirmation by medication use have previously proven to have even higher concordance with patients' medical records[53]. We did not take duration of somatic disease into account in the analyses. For cancer we accepted lifetime diagnosis, because in previous research depression and anxiety were consistently present for up to ten years among cancer survivors[54]. The low percentage after medication confirmation indicates that there is considerable uncertainty around this estimate.

In sum, the results of our study indicate that musculoskeletal disease and diabetes influence the course of depression and anxiety negatively, whereas other specific somatic diseases do not. Our results suggest that special attention should be paid to patients with a depressive or

anxiety disorder when diabetes or musculoskeletal disease are present. Since the prevalence of both arthritis and diabetes will probably continue to rise in the aging population over the next decades, managing these diseases optimally is of great clinical importance. In studies, concerning treatment of depression in somatically ill patients, antidepressants and psychological treatment might have a positive influence on course of depression[7;55;56]. More complex care models such as collaborative care in patients with somatic disease and depression may result in improved somatic disease control, less severe depressive or anxiety symptoms and better quality of life compared to usual care, also particularly in diabetes and arthritis patients, but at considerable costs[57-59]. Further treatment trials are necessary to find optimal strategies in managing depression and anxiety in patients also suffering from chronic somatic diseases, especially those with musculoskeletal disease and diabetes.

REFERENCE LIST

1. Bisschop MI, Kriegsman DM, Deeg DJ, Beekman AT, van Tilburg W. The longitudinal relation between chronic diseases and depression in older persons in the community: the Longitudinal Aging Study Amsterdam. *J Clin Epidemiol* 2004;57:187-194.
2. Geerlings SW, Beekman AT, Deeg DJ, van Tilburg W. Physical health and the onset and persistence of depression in older adults: an eight-wave prospective community-based study. *Psychol Med* 2000;30:369-380.
3. Harter M, Baumeister H, Reuter K et al. Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychother Psychosom* 2007;76:354-360.
4. Penninx BW, Beekman AT, Ormel J et al. Psychological status among elderly people with chronic diseases: does type of disease play a part? *J Psychosom Res* 1996;40:521-534.
5. Scott KM, Bruffaerts R, Tsang A et al. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. *J Affect Disord* 2007;103:113-120.
6. Furedi J, Rozsa S, Zambori J, Szadoczky E. The role of symptoms in the recognition of mental health disorders in primary care. *Psychosomatics* 2003;44:402-406.
7. Losifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. *Curr Psychiatry Rep* 2004;6:193-201.
8. Nuyen J, Spreeuwenberg PM, Van Dijk L, van den Bos GA, Groenewegen PP, Schellevis FG. The influence of specific chronic somatic conditions on the care for co-morbid depression in general practice. *Psychol Med* 2008;38:265-277.
9. Buist-Bouwman MA, Ormel J, de Graaf R, Vollebergh WA. Functioning after a major depressive episode: complete or incomplete recovery? *J Affect Disord* 2004;82:363-371.
10. Buist-Bouwman MA, de Graaf R, Vollebergh WA, Ormel J. Comorbidity of physical and mental disorders and the effect on work-loss days. *Acta Psychiatr Scand* 2005;111:436-443.
11. Sareen J, Jacobi F, Cox BJ, Belik SL, Clara I, Stein MB. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. *Arch Intern Med* 2006;166:2109-2116.
12. Wells KB, Stewart A, Hays RD et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA* 1989;262:914-919.
13. Bremmer MA, Beekman AT, Deeg DJ et al. Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord* 2008;106:249-255.
14. Vogelzangs N, Beekman AT, Boelhouwer IG et al. Metabolic depression: a chronic depressive subtype? findings from the InCHIANTI study of older persons. *J Clin Psychiatry* 2011;72:598-604.
15. Beekman AT, Deeg DJ, Geerlings SW, Schoevers RA, Smit JH, van Tilburg W. Emergence and persistence of late life depression: a 3-year follow-up of the Longitudinal Aging Study Amsterdam. *J Affect Disord* 2001;65:131-138.
16. Kisely S, Simon G. An international study of the effect of physical ill health on psychiatric recovery in primary care. *Psychosom Med* 2005;67:116-122.
17. Lyness JM, Caine ED, King DA, Conwell Y, Duberstein PR, Cox C. Depressive disorders and symptoms in older primary care patients: one-year outcomes. *Am J Geriatr Psychiatry* 2002;10:275-282.

18. Sherbourne CD, Hays RD, Wells KB. Personal and psychosocial risk factors for physical and mental health outcomes and course of depression among depressed patients. *J Consult Clin Psychol* 1995;63:345-355.
19. Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord* 2004;81:231-240.
20. Swindle RW, Jr., Cronkite RC, Moos RH. Risk factors for sustained nonremission of depressive symptoms: a 4-year follow-up. *J Nerv Ment Dis* 1998;186:462-469.
21. Vuorilehto MS, Melartin TK, Isometsa ET. Course and outcome of depressive disorders in primary care: a prospective 18-month study. *Psychol Med* 2009;39:1697-1707.
22. Wells KB, Rogers W, Burnam MA, Camp P. Course of depression in patients with hypertension, myocardial infarction, or insulin-dependent diabetes. *Am J Psychiatry* 1993;150:632-638.
23. van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. *J Fam Pract* 2000;49:1113-1120.
24. Roy-Byrne PP, Davidson KW, Kessler RC et al. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* 2008;30:208-225.
25. Penninx BW, Beekman AT, Smit JH et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* 2008;17:121-140.
26. APA. Diagnostic and Statistical Manual of Mental Disorders. Fourth edition. 2001. Washington D.C., American Psychiatric Publishing.
27. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry* 1991;159:645-53, 658.
28. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994;28:57-84.
29. Lyketsos C, Nestadt G, Cwi J, Heithoff K, Eaton W. The life-chart method to describe the course of psychopathology. *Int J Methods Psychiatr Res* 1994;4:143-155.
30. Lamers F, Hoogendoorn A, Smit J et al. Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr Psychiatry* 2011.
31. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol* 1996;49:1407-1417.
32. WHO. Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Classification. 2007. Geneva, World Health Organization.
33. Penninx BW, Nolen WA, Lamers F et al. Two-year course of depressive and anxiety disorders: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord* 2011;133:76-85.
34. Scott KM, Von Korff M, Alonso J et al. Age patterns in the prevalence of DSM-IV depressive/anxiety disorders with and without physical co-morbidity. *Psychol Med* 2008;38:1659-1669.
35. van den Brink RH, Ormel J, Tiemens BG et al. Predictability of the one-year course of depression and generalized anxiety in primary care. *Gen Hosp Psychiatry* 2002;24:156-163.

36. Nicassio PM. Arthritis and psychiatric disorders: disentangling the relationship. *J Psychosom Res* 2010;68:183-185.
37. van 't Land H, Verdurmen J, Ten Have M, van Dorsselaer S, Beekman A, de Graaf R. The association between arthritis and psychiatric disorders; results from a longitudinal population-based study. *J Psychosom Res* 2010;68:187-193.
38. Verbrugge LM, Juarez L. Arthritis disability and heart disease disability. *Arthritis Rheum* 2008;59:1445-1457.
39. Axford J, Heron C, Ross F, Victor CR. Management of knee osteoarthritis in primary care: pain and depression are the major obstacles. *J Psychosom Res* 2008;64:461-467.
40. Vreeburg SA, Hoogendijk WJ, van Pelt J et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry* 2009;66:617-626.
41. Vreeburg SA, Zitman FG, van Pelt J. et al. Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosom Med* 2010;72:340-347.
42. Penninx BW, van Dyck R. [Depression and somatic comorbidity]. *Ned Tijdschr Geneeskd* 2010;154:A1784.
43. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry* 2008;65:1358-1367.
44. Licht CM, de Geus EJ, van Dyck R, Penninx BW. Association between anxiety disorders and heart rate variability in The Netherlands Study of Depression and Anxiety (NESDA). *Psychosom Med* 2009;71:508-518.
45. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry* 2004;55:1-9.
46. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 2000;23:1556-1562.
47. Adriaanse M, Bosmans J. Diabetes prevalence, diabetes regimen and co-morbidity in depressed patients compared with non-depressed patients in primary care in the Netherlands. *Diabetic Medicine* 2010;27:718-722.
48. Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. *Curr Opin Psychiatry* 2006;19:421-427.
49. Lustman PJ, Griffith LS, Freedland KE, Clouse RE. The course of major depression in diabetes. *Gen Hosp Psychiatry* 1997;19:138-143.
50. Pouwer F, Geelhoed-Duijvestijn P, Tack C et al. Original article: Education and psychological aspects. Prevalence of comorbid depression is high in out-patients with Type 1 or Type 2 diabetes mellitus. Results from three out-patient clinics in the Netherlands. *Diabetic Medicine* 2010;27:217-224.
51. Dirmaier J, Watzke B, Koch U et al. Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control. *Psychother Psychosom* 2010;79:172-178.
52. Grigsby AB, Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. Prevalence of anxiety in adults with diabetes: a systematic review. *J Psychosom Res* 2002;53:1053-1060.
53. Tisnado DM, Adams JL, Liu H et al. What is the concordance between the medical record and patient self-report as data sources for ambulatory care? *Med Care* 2006;44:132-140.

54. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors--a systematic review. *Int J Psychiatry Med* 2010;40:163-181.
55. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. *Cochrane Database Syst Rev* 2010;CD007503.
56. Beltman MW, Voshaar RC, Speckens AE. Cognitive-behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2010;197:11-19.
57. Katon WJ, Von Korff M, Lin EH et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry* 2004;61:1042-1049.
58. Katon WJ, Lin EH, Von Korff M et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;363:2611-2620.
59. Stiefel F, Zdrojewski C, Hadj F.B. et al. Effects of a multifaceted psychiatric intervention targeted for the complex medically ill: a randomized controlled trial. *Psychother Psychosom* 2008;77:247-256.