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## Functional disability as an explanation of the associations between chronic physical conditions and 12-month major depressive episode

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### Abstract

**Background**—The link between physical conditions and mental health is poorly understood. Functional disability could explain the association of physical conditions with major depressive episode (MDE) as an intermediary factor.

**Methods**—Data was analyzed from a subsample (N=8,796) of the European Study of the Epidemiology of Mental Disorders (ESEMeD), a cross-sectional general population survey. MDE during the last 12 months was assessed using a revision of the Composite International Diagnostic Interview (CIDI 3.0). Lifetime chronic physical conditions were assessed by self-report. Functional disability was measured using a version of the World Health Organization Disability

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Conflict of interest

All authors declare that have no conflicts of interest in submitting this paper.

Contributors

Mariken E. Stegmann wrote the first draft of the manuscript; Johan Ormel, Ron de Graaf, Josep-Maria Haro, Giovanni de Girolamo, Koen Demyttenaere, Vivianne Kovess, Herbert Matschinger, and Jordi Alonso critically revised the manuscript; Gemma Vilagut undertook the statistical analyses and Huibert Burger managed the literature searches and supervised the analyses. All authors contributed to and have approved the final manuscript.

Assessment Schedule (WHODAS). The associations of physical conditions with MDE and explanation by functional disability were quantified using logistic regression.

**Results**—All physical conditions were significantly associated with MDE. The increases in risk of MDE ranged from 30% for allergy to 100% for arthritis and heart disease. When adjusted for physical comorbidity, associations decreased and were no longer statistically significant for allergy and diabetes. Functional disability explained between 17 and 64% of these associations, most substantially for stomach or duodenum ulcer, arthritis and heart disease.

**Limitations**—Due to the cross-sectional nature of the study the temporal relationship of the variables could not be assessed and the amount of explanation can not simply be interpreted as the amount of mediation.

**Conclusions**—Our findings suggest that the association of chronic physical conditions with MDE is partly explained by functional disability. Such explanation is more pronounced for pain causing conditions and heart disease. Health professionals should be particularly aware of the increased risk of depressive disorder when patients experience disability from these conditions.

### Keywords

Major depressive episode; chronic physical conditions; disability

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### Introduction

According to the United Nations, 15.9 % of the European population was older than 65 years in 2005. This percentage is expected to grow to 27.6 by 2050. (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2008) Consequently, the already high prevalence of age-related chronic physical conditions like arthritis and diabetes mellitus will further increase. Improvement of medical treatments and general living conditions may promote this trend. (Hoffman et al., 1996) As a result the prevalence of depressive disorders is expected to rise as studies have consistently shown positive associations between chronic physical conditions and depressive disorder. (Buist-Bouwman et al., 2005; Ormel et al., 1997; Patten, 2001; Wells et al., 1988)

Although bidirectional relationships between physical conditions and depressive disorders may contribute to mental-physical comorbidity, (Ormel et al., 2002) the framework of the present study was restricted to physical conditions leading to a depressive disorder. For the explanation of this relationship, several theories have been coined. A prevailing theory is the pathophysiologic theory postulating that depression is caused by specific biological mechanisms involved in certain physical conditions, (Cohen et al., 1995) for example in vascular depression. (Alexopoulos et al., 1997) The cognitive theory, on the other hand, states that the actual cause of depression is the disability associated with a physical condition rather than its specific pathophysiology. (Katon, 2003) For example, Knol and colleagues suggested that it is the burden and potential disability from diabetes mellitus that causes depressive symptoms rather than a disturbed glucose homeostasis. (Knol et al., 2007) The cognitive theory agrees with the restricted activity model according to which restriction of normal activities mediates the association of physical disease with depression. (Williamson, 2000)

There have been few attempts to determine to what extent the cognitive theory holds, i.e. to what extent depressive disorders in subjects with a chronic physical condition can be explained by functional disability. (Prince et al., 1998) Most previous studies have focused on particular physical conditions, (Dunlop et al., 2004) or lumped physical conditions, (van Gool et al., 2005) thus limiting the possibility of drawing more general conclusions and

making it difficult to compare different physical conditions. Importantly, many studies that assessed multiple physical conditions did not adjust for the substantial co-morbidity of these conditions. (Patten, 2001; Prince, Harwood, Thomas, and Mann, 1998; Scott et al., 2007; Wells, Golding, and Burnam, 1988) This limits the possibility of comparing the independent contributions of individual conditions to the risk of depressive disorder as these conditions tend to co-occur in the same individuals. (Charlson et al., 2002) Finally, most studies were conducted in clinical samples rather than in the general population, possibly hampering their generalizability. (Katon et al., 2007)

The aim of the present study was to determine the association of seven specific chronic physical conditions with 12-month major depressive episode (MDE), independent from physical comorbidity. Further, we aimed to assess to what extent these associations can be explained by functional disability and whether the amount of explanation depends on the specific physical condition. The analyses were carried out using data from a large European general population survey.

## Methods

The European Study of the Epidemiology of Mental Disorders (ESEMeD) (Alonso et al., 2002) is a large cross-sectional study conducted in six European countries which is part of the WHO (World Health Organisation) World Mental Health (WMH) Survey Initiative. (Alonso et al., 2004a)

### Sample and measures

A stratified, multistage, clustered area, probability sample design was used. The target population consisted of the non-institutionalized adult population aged 18 years or older of Belgium, France, Germany, Italy, the Netherlands and Spain, in total 212 000 000 Europeans. In order to optimize the interviewing process and cost, a two-phase interview procedure was used in the questionnaire. The first phase of the interview was administered to all respondents and contained the diagnostic assessment of the most common mood and anxiety disorders, health related quality of life, health services utilization and main demographic characteristics. In total, 21,425 individuals were interviewed between January 2001 and August 2003. The overall response rate in the six countries was 61.2%, with the highest rates in Spain (78.6%) and Italy (71.2%) and lowest rates in Germany (57.8%), the Netherlands (56.4%), Belgium (50.6%) and France (45.9%). The interviews were performed by trained persons using a computer assisted personal interview (CAPI) that included the CIDI 3.0, a modified version of the Composite International Diagnostic Interview (CIDI), (Wittchen, 1994) developed by the WMH Survey Consortium. (Kessler et al., 2004) CIDI is a widely used interview in epidemiological studies on mental disorders generating DSM-IV (Diagnostic Statistical Manual of Mental Disorders) diagnoses. More information can be found elsewhere. (Alonso et al., 2004b).

Only those who exceeded a number of symptoms of specific mood or anxiety disorders (N=4,246) and a random 25% (N=4,550) of the remainder were asked the second phase of the questionnaire (8,796 in total). Analyses for the present study were based on this second phase sample, which is representative of the populations of the six countries because weights were applied to correct for the probability of selection for stage 2. The second phase included, among other information, a standard chronic physical condition checklist of the kind commonly used in national health surveys. (National Center for Health Statistics, 1994) Using this checklist, respondents reported if they ever had arthritis or whether they had ever been told by a physician or other health professional they had heart disease, high blood pressure, asthma, diabetes mellitus or an ulcer in their stomach or intestine. Research has demonstrated reasonable correspondence between self-reported chronic conditions and

general practitioner records.(Kehoe et al., 1994;Kriegsman et al., 1996) Because of the low prevalence of stroke (1.3%), this condition was not analysed. Headache and low back pain fall outside the scope of the present study because they can not be considered specific chronic physical conditions.

Functional disability was defined as days out of role measured by the role functioning subscale score of the World Health Organization Disability Assessment Schedule (WHODAS) version used in ESEMeD, the ESEMeD WHODAS.(Alonso et al. 2004b) This score is based on responses to four questions about the number of days the respondent was completely unable to work or carry out his normal activities, had to cut down the quantity or quality of activities, or had to apply extreme effort to perform at the usual level because of physical health, mental health, or substance use problems in the past 30 days. Scores 1, 0.5 and 0.25 were assigned for each day a respondent was completely out of role, had to cut down activities or had to apply extreme effort, respectively. Its sum, transformed to a 0–100 scale, was the days out of role score used in the analyses. Psychometric detail on this version of the ESEMeD WHODAS is given elsewhere.(Buist-Bouwman et al., 2008)

In addition to age and gender, income and marital status were documented. Income was scored as country-specific quartiles. For the present analysis marital status was coded as a dichotomous variable: either married or cohabiting, or otherwise.

To prevent reverse causality as much as possible, the analyses were conducted for 12-month MDE, i.e. those that were present in the year before the interview only. Out of a total of 8,796 respondents, 2, 082 individuals with a history of MDE more than 12 months before the interview were excluded leaving 6,714 individuals for the analyses.

## Data analysis

Demographics and functional disability were compared between individuals with and without a MDE using the  $\chi^2$  test for categorical variables and the Mann-Whitney U test for continuous variables. Resulting p-values were adjusted for multiple comparisons using the Bonferroni method.

Associations were analyzed using logistic regression and odds ratios (ORs) with 95% confidence intervals (CIs) as measures of relative risk were reported.

The association between the number of physical conditions on a person level and MDE was analyzed in two ways. First, the number of conditions was entered as a categorical independent variable. Second, we tested for a trend in the association with MDE by entering the number of conditions as a continuous independent variable.

Subsequently, the independent associations between each physical condition and being out of role were estimated with and without adjustment for the presence of all other physical conditions. The adjustments were made to account for the potential co-morbidity of physical conditions. In these analyses, being out of role was arbitrarily defined as a days out of role score greater than zero.

Next, the associations between each physical condition and a MDE were quantified, again with and without adjustment for the presence of all other physical conditions.

The explanation of the independent association between chronic physical conditions and MDE by functional disability was investigated in two steps. First, we investigated whether functional disability was a predictor of MDE in the total study population and in those without a physical condition. Second, we assessed the decrease in the OR for each physical condition when adjusting for days out of role as a continuous variable. The relative decrease

can be considered a measure of explanation by functional disability and was expressed as a percentage of the OR while not adjusting for days out of role. This analysis was restricted to those physical conditions that showed a statistically significant and independent association with MDE.

All ORs were adjusted for potential confounders: gender, age, income and marital status. Goodness of fit of the logistic models was assessed using the Hosmer-Lemeshow test. Statistical significance of this test indicates lack of sufficient model fit.

Individuals were weighted to account for the different probabilities of selection, the two-stage design, as well as to restore the age and gender distribution of the population within each country and the relative dimension of the population across countries. (Alonso, et al. 2004b) The two-sided level of significance was set at 0.05. SPSS (Statistical Package for the Social Sciences 12.0.1) and STATA 7.0 were used for the analyses.

## Results

Approximately one in twenty respondents reported a 12-month MDE. They were more often female, younger, in the lowest income category, not married or cohabiting and were more often out of role compared to those without MDE (Table 1).

The prevalence of physical co-morbidity was high with 18% respondents having reported more than one physical condition. With each increase in the number of chronic physical conditions the presence of MDE became more likely, up to an ample five times in case of four or more physical conditions compared to none (Table 2). The association was graded, there was no threshold, and the trend was statistically significant with  $P < 0.001$ .

Figure 1 demonstrates a higher prevalence of MDE in the presence of each individual physical condition compared to its absence.

In table 3 the associations of physical conditions with being out of role are portrayed. They were all statistically significant. The strongest associations were observed for arthritis, heart disease and stomach/duodenum ulcer with relative risks exceeding two. The associations of physical conditions with being out of role were largely independent of each other as for each condition, adjustment for the remaining conditions made the ORs drop only a little. Nevertheless, associations were no longer statistically significant for hypertension, asthma and diabetes mellitus.

The increases in likelihood of MDE in the presence of a chronic physical condition ranged from around 30% for allergy to ample 100% for arthritis and heart disease and were all statistically significant (Table 4). When physical conditions were mutually adjusted to study their independent associations with MDE, the ORs were smaller and no longer statistically significant for allergy and diabetes.

An out of role score greater than zero was strongly associated with MDE with ORs (95%CI) of 4.37 (3.52 – 5.43) and 4.33 (3.10 – 6.04) amongst the total population and among those without a physical condition, respectively.

When we additionally adjusted for the number of days out of role, as a way of assessing explanation by this variable, substantial decreases in the associations with MDE were observed. Decreases regarded all physical conditions except for allergy. They were particularly pronounced for arthritis, heart disease and stomach/duodenum ulcer. Statistically significant associations with MDE remained for arthritis and hypertension only.

None of the Hosmer-Lemeshow tests was statistically significant, indicating no lack of model fit. Controlling for country did not change any of the results materially.

## Discussion

In the present large population-based study we observed substantial associations of the majority of chronic physical conditions with the presence of 12-month MDE. All associations decreased when adjusted for physical comorbidity. The risk of MDE was steeply and positively related to the number of physical conditions in a dose-response manner. Functional disability explained associations of physical conditions with MDE for between 17 and 64%. Such an explanation was most marked for arthritis, heart disease and stomach/duodenum ulcer. Our study confirms the well-known association between chronic physical disorders and depression. The specific contribution of the present study to the literature is twofold. First, we compared the amount of explanation by functional disability between physical conditions in one survey. Second, the association of each physical condition with MDE was assessed independent of the presence of co-morbid physical conditions.

The findings in this study should be interpreted in consideration of some limitations. We used self-reports to assess the presence of chronic physical conditions and this may have introduced misclassification. However, self-reports on physical conditions generally have shown good correspondence to diagnoses from medical records.(Kehoe, Wu, Leske, and Chylack, Jr., 1994;Kriegsman, Penninx, van Eijk, Boeke, and Deeg, 1996) Yet, the degree of correspondence may depend on the specific condition and has been found excellent in diabetes, fair to good in heart disease, and poor in arthritis.(Simpson et al., 2004) Importantly, depressive symptoms do not seem to affect self-report of diagnosed physical conditions in a systematic way.(Kolk et al., 2002)

Second, no strong inferences as to the direction of the associations between chronic physical conditions, functional disability and 12-month MDE can be made. Although we excluded persons with a lifetime depressive disorder without a 12-month MDE diagnosis, reverse causality is hard to exclude.(Cohen and Rodriguez, 1995) Because virtually all physical conditions were associated with MDE it is in our view unlikely that pre-existing depression was more often the cause rather than the consequence of the physical conditions. This is because we assume that it is unlikely that depression is a generic risk factor, i.e. a risk factor for all physical conditions. Notably, a bidirectional association is most likely.(Ormel, Rijdsdijk, Sullivan, van, and Kempen, 2002) The functional disability measure in our study concerned the last 30 days only and could not exclusively be attributed to the physical conditions. It is unknown to what extent it can be generalized to the period before the MDE developed. The direction of the relation between disability and MDE is therefore uncertain and interpretation of the analyses on the amount of explanation by disability should be cautious and should not be simply interpreted as the amount of mediation.

Strong points of this study include the large sample size, the inclusion of a general population sample, the assessment of the explanatory role of functional disability and the adjustment of the association of each physical condition for the presence of each individual co-morbid physical condition.

Our findings support the cognitive theory suggesting substantial explanation, possibly mediation, of the relation between chronic physical conditions and depression by limitations in role functioning. This fits with the theory that decrements in normal activities are a likely factor in the development of depression, i.e. the restriction model of depressed affect. (Williamson, 2000)

Notably, the amount of explanation by role functioning varied substantially with the specific physical condition. It was most pronounced for those conditions that were also most substantially associated with being out of role, i.e. arthritis, heart disease and stomach or duodenum ulcer. For arthritis and stomach or duodenum ulcer, the strong explanation by limitations in role functioning may be explained by their association with pain. Previous research has shown that painful symptoms from physical conditions are firmly associated with reductions in role functioning and depression.(Bair et al., 2003) For heart disease, the strong explanation by limitations in role functioning cannot fully be explained by pain. Although heart disease may be associated with pain in case of myocardial ischaemia, many heart disease patients suffer from heart failure which is not a pain condition. Yet, the decreased cardiac output in heart failure is commonly associated with poor physical function which, in turn, may be associated with depressed mood and loss of interest.(Thomas et al., 2008)

The strong explanation for specifically arthritis and heart disease concurs with the findings from two comparable studies.(Dunlop, Lyons, Manheim, Song, and Chang, 2004;Ormel, Kempen, Penninx, Brilman, Beekman, and van, 1997) The study by Dunlop and colleagues, however, did not compare the extent of explanation with other physical conditions. The associations of arthritis and hypertension with MDE in the present study remained significant when adjusted for functional disability. This was also noticed by Dunlop et al. in their study and suggests that other pathways, e.g. pathophysiologic pathways, co-exist. Explanation by functional disability was minor for hypertension and asthma. Although this can be explained for hypertension by its absence of symptoms, it seems hard to explain this for asthma which is known to be associated with considerable functional disability. (Mannino, 2005) Allergy and diabetes did not show independent associations with MDE in the present study. This is surprising given the associations of these physical conditions with depression reported in the literature.(Anderson et al., 2001;Goodwin et al., 2006). Confounding by physical comorbidity might be an explanation as the analyses without comorbidity adjustment in our study did show significant associations with MDE. This type of confounding may also have played a role in a meta-analysis showing a two times higher risk in persons with diabetes as compared to those without this condition as no adjustments were made for coexisting physical conditions.(Anderson, Freedland, Clouse, and Lustman, 2001)

The observation that in our study physical co-morbidity was highly prevalent and that for each condition the association with MDE substantially reduced when we accounted for the presence of all other physical conditions suggests that associations of specific individual physical conditions with depressive disorders are not independent. Therefore, previous studies may have overestimated the association of individual physical conditions with depression.(Charlson and Peterson, 2002)

A clinical implication of the results of the present study may be that health professionals should be particularly alert on the development of depressive disorder when patients experience substantial disability from arthritis, heart disease, or stomach/duodenum ulcer. If the associations are causal, reducing disability from these physical conditions, for instance by pain control, may aid in preventing depressive disorder.

A research implication of our findings is that future similar studies should adjust for physical comorbidity to investigate individual contributions of physical conditions to the risk of depression.

In conclusion, our findings show that the association of chronic physical conditions with MDE can be explained by functional disability to an extent that strongly depends on the

specific condition. Explanation is most substantial for chronic conditions with painful symptoms and heart disease. Health professionals should be particularly aware of the increased risk of depressive disorder when patients experience disability from these conditions.

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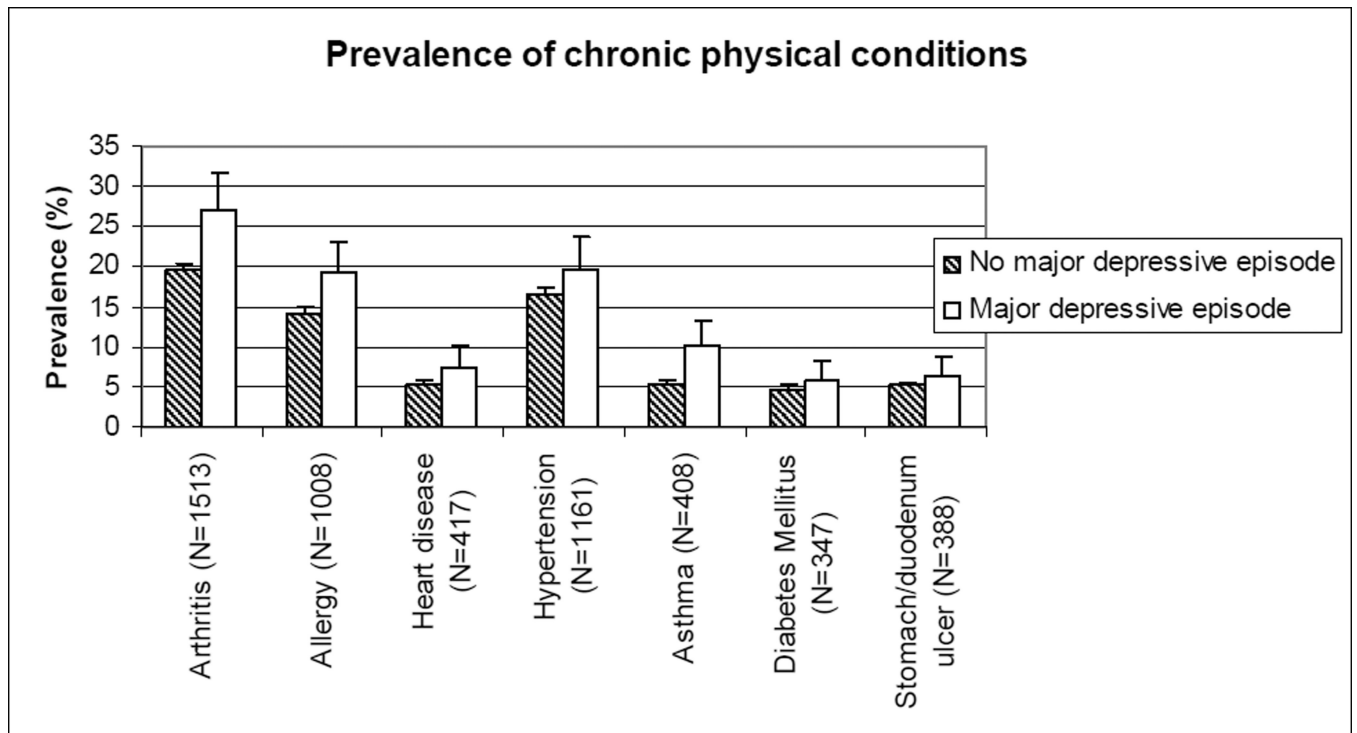
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**Figure 1.**

Prevalence of chronic physical conditions in persons with a 12-month major depressive episode (N=905) and without (N=5,809) a major depressive episode lifetime N's are unweighted. Prevalences are weighted to obtain representativeness of the figures for the European populations. Weights take into account the different probabilities of selection, the two-stage design and restore the age and gender distribution of the population within each country and the relative dimension of the population across countries.

**Table 1**

Characteristics of the ESEMeD project, phase 2, in which a standard chronic physical condition checklist was administered.

<b>Total</b>	<b>No major depressive episode lifetime</b>	<b>12-month major depressive episode</b>	<b>p-value</b>
<b>N = 6,714</b>	<b>N= 5,809 (95%)</b>	<b>N=905 (5%)</b>	
Male gender	51%	33%	< 0.005
Mean age (min; max)	47.3 (18; 97)	43.0 (18; 89)	< 0.005
Income quartile 1 (range: 1–4)	19%	26%	0.005
Marital status married/cohabiting	68%	55%	< 0.005
Days out of role score > 0 *	16%	45%	< 0.005

N's are unweighted. Mean and proportions are weighted to obtain representativeness of the figures for the European populations. Weights take into account the different probabilities of selection, the two-stage design and restore the age and gender distribution of the population within each country and the relative dimension of the population across countries.

\* Dichotomized because of extreme skewness.

P-values are from  $\chi^2$  tests for gender and marital status and from Mann-Whitney U tests otherwise.

**Table 2**

Odds ratios (OR) with 95% confidence intervals (CI) of suffering a 12-month major depressive episode for those with one or more chronic physical conditions (compared to those with no physical condition)

Number of physical conditions (%)	OR (95%-CI) *
Zero (54%)	1
One (28%)	1.50 (1.17–1.94)
Two (13%)	2.02 (1.50–2.79)
Three (4%)	3.50 (2.24–5.48)
Four or more (1%)	5.62 (2.88–10.97)

Proportions are weighted to obtain representativeness of the figures for the European populations. Weights take into account the different probabilities of selection, the two-stage design and restore the age and gender distribution of the population within each country and the relative dimension of the population across countries. ORs are adjusted for age, gender, income and marital status.

\* P for trend: < 0.001

**Table 3**

Relative risk of being out of role (days out of role score > 0) for the presence of specific physical conditions, expressed as odds ratios (OR) with 95% confidence intervals (95% CI), adjusted for age, gender, income and marital status

<b>Chronic physical condition (Unweighted N)</b>	<b>OR (95%CI)</b>	<b>OR (95%CI)*</b>
Arthritis (N=1513)	2.40 (1.93–2.98)	2.28 (1.83–2.84)
Allergy (N=1008)	1.47 (1.16–1.87)	1.32 (1.02–1.69)
Heart disease (N=417)	2.53 (1.77–3.63)	2.21 (1.54–3.17)
Hypertension (N=1 161)	1.41 (1.09–1.82)	1.16 (0.89–1.51)
Asthma (N=408)	1.74 (1.24–2.43)	1.38 (0.98–1.96)
Diabetes mellitus (N=347)	1.61 (1.06–2.45)	1.46 (0.96–2.23)
Stomach/duodenum ulcer (N=388)	2.28 (1.59–3.27)	1.96 (1.38–2.78)

\* ORs are further adjusted for the presence of each remaining physical condition

**Table 4**

Relative risk of major depressive episode for the presence of specific physical conditions, expressed as odds ratios (OR) with 95% confidence intervals (95%CI), adjusted for age, gender, income and marital status

Chronic physical condition (Unweighted N)	OR (95%CI)	OR (95%CI) *	OR (95%CI) * † (decrease % of OR*)
Arthritis (N=1513)	2.10 (1.60–2.74)	1.94 (1.48–2.53)	1.50 (1.11–2.03) (–47%)
Allergy (N=1008)	1.31 (1.02–1.69)	1.14 (0.86–1.50)	-
Heart disease (N=417)	2.09 (1.41–3.11)	1.68 (1.11–2.54)	1.29 (0.79–2.11) (–57%)
Hypertension (N=1 161)	1.69 (1.29–2.22)	1.42 (1.07–1.88)	1.35 (1.00–1.83) (–17%)
Asthma (N=408)	1.92 (1.27–2.92)	1.68 (1.07–2.61)	1.53 (0.96–2.43) (–22%)
Diabetes mellitus (N=347)	1.70 (1.10–2.62)	1.40 (0.89–2.21)	-
Stomach/duodenum ulcer (N=388)	1.69 (1.19–2.40)	1.44 (1.00–2.08)	1.16 (0.76–1.78) (–64%)

\* ORs are further adjusted for the presence of each remaining physical condition

† ORs are additionally adjusted for days out of role score. OR and percentage decrease was not calculated when OR\* was not statistically significant