

Review articles

# Negative association of concomitant physical symptoms with the course of major depressive disorder: A systematic review

Klaas M.L. Huijbregts<sup>a,b,\*</sup>, Christina M. van der Feltz-Cornelis<sup>a,d,e</sup>,  
Harm W.J. van Marwijk<sup>b</sup>, Fransina J. de Jong<sup>a,b</sup>,  
Daniëlle A.W.M. van der Windt<sup>b,c</sup>, Aartjan T.F. Beekman<sup>d</sup>

<sup>a</sup>Department of Diagnosis and Treatment, Netherlands Institute of Mental Health and Addiction (Trimbos Institute), Utrecht, The Netherlands

<sup>b</sup>Department of General Practice and the EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

<sup>c</sup>Arthritis Research Campaign National Primary Care Centre, Keele University, Keele, United Kingdom

<sup>d</sup>Department of Psychiatry and the EMGO+ Institute for Health and Care Research, VU University Medical Care Center, Amsterdam, The Netherlands

<sup>e</sup>Department of Clinical and Developmental Psychology, University of Tilburg, Tilburg, The Netherlands

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## Abstract

**Objective:** The prognosis of depression greatly varies among patients, and the physical symptoms that often accompany depression may predict treatment resistance and a worse outcome. If so, this may have important clinical implications. The aim of this systematic review was to explore the association of concomitant physical symptoms with the outcome of major depressive disorder (MDD). **Methods:** Systematic review: Medline, Psychinfo, and the Cochrane Library were searched for prospective, cross-sectional, and retrospective studies, and also for open-label trials and randomized controlled trials. The risk of bias assessment and data extraction were performed in duplicate. A qualitative best-evidence synthesis was performed, based on the number of studies reporting on the association between physical symptoms and the course of

MDD, the consistency of the results, and the methodological quality. The findings were reported according to the PRISMA guidelines. **Results:** Nine studies met the inclusion criteria. Although the design, outcome measures, and data presentation varied too much to make statistical pooling possible, the best evidence synthesis resulted in strong, consistent evidence for a negative association between physical symptoms and the course of MDD. **Conclusion:** This systematic review shows a negative association of concomitant physical symptoms with the course of MDD. The effect might be considerable, but the number of studies addressing this topic is small and there was a wide variation in the study designs and outcome measures. More research is needed.

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**Keywords:** Depression; Comorbidity; Effect modifiers (epidemiology); Somatisation; Systematic review; Physical symptoms

## Introduction

The Global Burden of Disease Study, carried out by the WHO, reports that major depressive disorder (MDD) is expected to be the second leading cause of disability-adjusted life-years in 2020 [1]. Both psychological and pharmacological interventions are effective in the treatment of

MDD, but like in other fields of medicine, efficacy trials where it is possible to control certain conditions, do not always produce the same results as effectiveness trials in real world settings [2]. Results from the STAR\*D study, for instance, show that remission rates in response to treatment with a selective serotonin reuptake inhibitor (SSRI) are as low as 26.6% in primary care [3]. These rates improve after subsequent treatment steps, but remission is not easily achieved [4]. This might lead to unnecessary suffering and high costs for society [5,6].

MDD may be difficult to treat in everyday practice, as a result of concomitant physical symptoms interfering with

\* Corresponding author. Department of Diagnosis and Treatment, Netherlands Institute of Mental Health and Addiction (Trimbos Institute), PO Box 725, 3500 AS Utrecht, The Netherlands. Tel.: +31 30 2971185; fax: +31 30 2971111.

E-mail address: [khuijbregts@trimbos.nl](mailto:khuijbregts@trimbos.nl) (K.M.L. Huijbregts).

the course, or because depressed patients who experience many physical symptoms may be less motivated to undergo treatment. This is an important subject for study, in view of the frequent co-occurrence of physical symptoms and MDD. Studies in primary care, for instance, have found that up to 70% of MDD patients only report physical symptoms when first presenting to a general practitioner [7]. Moreover, a recent study [8] reported that it is 4.43 times more likely for a depressed patients to have a somatoform disorder than for patient who is not depressed (confidence interval: 2.73–7.19).

Examples of symptoms that often co-occur with MDD are pain, fatigue, disturbed sleep, indigestion, dizziness, and fainting [9,10]. The more of these symptoms a patient experiences, the greater the probability that he or she is also suffering from a depressive disorder [9,10]. The importance of physical symptoms in patients suffering from MDD will also be recognized by clinicians, many of whom find patients with physical comorbidity difficult to treat. A recent systematic review provided evidence that pain predicts a longer time to remission in patients suffering from MDD [11].

To our knowledge, evidence with regard to the prognostic effect of the wider spectrum of concomitant physical symptoms—not restricted to pain—on the course of MDD has not yet been reviewed. Identifying factors that may predict treatment resistance or poor outcome are important, both for the education of patients and the selection of appropriate treatment. We therefore conducted a systematic review of studies that assessed the associations between physical symptoms and the prognosis of MDD. The association in terms of prognostic value in cohort studies, as well as the modification of treatment effect in trials can provide valuable information about this topic. Both types of studies were therefore included.

## Method

### *Information sources and eligibility criteria*

The search was performed in Medline, Psychinfo, and the database of the Cochrane Collaboration. The search focused on retrospective and prospective designs, as well as on open-label trials and randomized controlled trials. Studies had to meet the following criteria in order to be included:

1. At baseline, an assessment had to be made to determine whether patients were suffering from MDD. There was no restriction as to how MDD was diagnosed. At follow-up, an assessment had to be made about the outcome of the disorder. This could include clinical outcomes such as symptom reduction on a scale measuring depressive symptoms, response in terms of a decrease of a certain percentage on a scale measuring depressive symptoms, and time to such a response.

It could also include process measures such as treatment adherence.

2. An assessment of physical symptoms had to be included at baseline. Since this review focused on a wider spectrum of physical symptoms than just one individual symptom, such as pain, special attention was paid to the way in which these symptoms were identified. The assessment of physical symptoms at baseline could not be limited to just one symptom. Furthermore, the studies had to include either:
  - (a) a validated (sub-)scale to measure physical symptoms
  - (b) information about physical symptoms from medical records
  - (c) an assessment of physical symptoms by a medical practitioner.

With regard to the sub-criterion (a) (validated measures), we decided that the anxiety/somatization sub-scale of the Hamilton Depression Inventory 17-item version (HAM-D-17) [12] could not be used as a valid measure of physical symptoms for the purpose of our review. This sub-scale consists of six items that reflect on both psychological and somatic symptoms of depression and anxiety. Therefore, studies had to use some other instrument to assess physical symptoms.

3. Studies had to report sufficient information on the association between physical symptoms and the outcome or course of MDD, expressed as odds ratios (OR), relative risks (RR), beta-coefficients ( $\beta$ ), hazard ratios (HR), effect sizes, or mean differences.

### *Search*

The exact keywords and Mesh-terms are available upon request. Briefly, we combined multiple keywords and medical subject headings (Mesh-terms) for MDD with multiple keywords regarding information on the outcome or course of the disorder and keywords referring to the design of the study. Finally, 102 symptoms and symptom-related keywords were added to the search, ranging from pain and fatigue to somatoform disorders or somatization, and including symptoms such as headache, nausea, and gas. Our search strategy is described in more detail in the Appendix.

The following searches were conducted:

- Medline was searched from its onset to November 24, 2008. There was no restriction as to the publication date of a study. The searches in Medline were periodically updated after the 24th of November 2008, but no additional papers were identified before submission of this document. There was no language restriction included in the search.
- Psychinfo was searched until March 25, 2009. Again, there was no restriction with regard to publication date or language.

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