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Review article

Medically unexplained symptoms, somatisation disorder and hypochondriasis: Course and prognosis. A systematic review☆,☆☆

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Abstract

Objective: To study the course of medically unexplained symptoms (MUS), somatisation disorder, and hypochondriasis, and related prognostic factors. Knowledge of prognostic factors in patients presenting persistent MUS might improve our understanding of the naturalistic course and the identification of patients with a high risk of a chronic course. **Methods:** A comprehensive search of Medline, PsycInfo, CINAHL, and EMBASE was performed to select studies focusing on patients with MUS, somatisation disorder, and hypochondriasis, and assessing prognostic factors. Studies focusing on patients with single-symptom unexplained disorder or distinctive functional somatic syndromes were excluded. A best-evidence synthesis for the interpretation of results was used. **Results:** Only six studies on MUS, six studies on hypochondriasis, and one study on abridged somatisation could be included. Approximately 50% to 75% of the patients with MUS improve, whereas 10% to 30% of patients with MUS deteriorate. In patients with hypochondriasis, recovery rates vary between 30% and 50%. In studies on MUS and hypochondriasis, we found some evidence that the number of somatic symptoms at baseline influences the course of these conditions. Furthermore, the seriousness of the condition at baseline seemed to influence the prognosis. Comorbid anxiety and depression do not seem to predict the course of hypochondriasis. **Conclusions:** Due to the limited numbers of studies and their high heterogeneity, there is a lack of rigorous empirical evidence to identify relevant prognostic factors in patients presenting persistent MUS. However, it seems that a more serious condition at baseline is associated with a worse outcome.

Keywords: Medically unexplained symptoms; Hypochondriasis; Somatoform disorders; Prognosis; Course

Introduction

Medically unexplained symptoms (MUS) are common in primary care [1]. In 25–50% of all primary care visits, no somatic cause is found to explain the patient's presenting symptoms [2]. It is generally believed that persistent presentation of MUS is a chronic and disabling disorder [3]. However, in many patients MUS are transient and have a good prognosis. A recent Dutch study found that only 2.5% of the attendees in general practice presenting with such symptoms meet criteria for chronicity [4].

In a recent review, researchers stated that in population-based and primary care samples, MUS is the common characteristic of the *DSM-IV* and *ICD-10* somatoform disorders including somatisation and hypochondriasis [5–7]. Somatisation is characterized by recurrent and frequent presentation of MUS, whereas hypochondriasis is characterized by excessive worry about illness and the belief of having an undiagnosed physical disease.

Despite the low prevalence of persistent MUS, it represents a serious problem in primary care. Patients are functionally impaired, have high rates of comorbid psychiatric disorders, and are at risk for unnecessary, potentially harmful diagnostic

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procedures and treatments [2,3,8]. Moreover, part of the burden to GPs are the difficulties in explaining the symptoms, finding a shared understanding necessary to reach reassurance and acceptation of the symptoms, and the lack of treatment options [9,10]. Often, GPs label these patients as 'heartsink patients' or 'helpoholic patients' [11]. For patients, as well as GPs and the health care system, it is important to prevent persistent MUS. Therefore, GPs should be able to recognize patients with a high risk of persistent MUS. However, GPs experience difficulties in distinguishing self-limiting MUS from persistent MUS [12]. Knowledge of prognostic factors may improve our management of patients with MUS, as patients with a good prognosis can be reassured about the favourable spontaneous recovery rates, whereas a more intensive approach including some form of reattribution or cognitive behavioural therapy might be indicated from the beginning in the high-risk groups.

The aim of our study was to gain an insight into the course of MUS and in factors influencing its course.

Method

Data sources and search strategy

We systematically reviewed prospective cohort studies in primary, secondary, or tertiary care on patients with MUS, somatoform disorders, and hypochondriasis. We studied somatisation disorder, MUS, and hypochondriasis together because they appear to have much in common: medically unexplained symptoms, typical illness and sick role behaviour, disproportionate disability, and preoccupation with health and illness [7].

Although there are many other general terms to describe physical symptoms without an organic explanation, we use the term 'medically unexplained symptoms' as none of these terms are ideal and this is the most neutral description [13,14].

We did not include clinical trials in this review as the patients recruited into trials are often not representative of the population with the disorder [15,16]. Moreover, participating in a trial can influence the natural course of the symptoms as participating in a trial can be considered as an intervention in itself.

We searched in the MEDLINE database for publications published between 1965 and 1 June 2006, in PsycINFO between 1967 and 1 June 2006, in CINAHL between 1982 and 1 June 2006, and in EMBASE between 1965 and 1 June 2006. We obtained additional references from the reference lists of review articles and retrieved original papers. We used the following keywords: somatoform disorder, hypochondriasis, neurasthenia, conversion disorder, psychophysiological disorder, functional somatic sympt*, and medically unexplained*.

We combined this search using the Boolean operator AND with the sensitive MEDLINE search for clinical studies on prognosis [17]. The search strategy is shown in Appendix A. There were no limitations regarding the language of publication. We tested the search strategy on 30 publications about medically unexplained symptoms in our own database and found the search strategy to be sensitive as all known articles were found.

Study selection

TOH and MB independently screened the titles and abstracts of all identified citations to identify eligible articles. When we could not decide on inclusion, we consulted the full publication.

If after studying the complete manuscript disagreement persisted, we consulted a third reviewer (FvdL). We used Cohen's kappa statistic (κ) to assess agreement between the two reviewers [18]. Inclusion criteria were prospective cohort design, focus on prognosis of patients with medically unexplained symptoms, and a follow-up of 3 months or more.

We excluded studies that focused primarily on patients with medical or psychiatric disease (except somatoform disorders and hypochondriasis). We also excluded studies that focused on patients suffering from single-symptom unexplained disorder (tension headaches, dysmenorrhoea) or patients suffering from distinctive functional somatic syndromes (irritable bowel syndrome, chronic fatigue syndrome) because we were interested in the course and prognosis of undifferentiated medically unexplained symptoms. We focused on undifferentiated MUS as we assume that these are more difficult to handle for the physician than single symptom unexplained disorders and distinctive functional syndromes. After all, the latter give more opportunity to explain the symptoms to patients. Finally, there is evidence that the name of a condition influences prognosis [19]. Studies on children and adolescents (age <18 years) and studies on specific groups of patients such as refugees, street prostitutes, etc., were excluded. Case-control studies, cross-sectional studies, and case studies were also excluded.

Data extraction

Two reviewers (ToH and MB) independently scored the methodological quality of the included studies. We used a standardized checklist of predefined criteria (see Appendix B), which has been used in previous prognostic reviews [20,21]. The list is based on theoretical considerations and methodological aspects described by Hudak et al. [22] and Altman [23]. We modified these checklists according to new insights [24]. We tested the quality assessment checklist in a pilot assessment. A detailed explanation of each criterion is given in Appendix C. Each criterion was scored positive (+), negative (−), or unclear (?). The total quality score is the sum of all the criteria that are scored positive. The maximum quality score is 21. We calculated the quality of a study as the percentage of the maximum score.

We discussed disagreements in the scoring of quality items in a consensus meeting. In case of persistent

disagreement between the two reviewers, a third reviewer (FvdL) made the final decision.

We categorized quality criteria into four major forms of bias: selection bias, completeness of follow-up, information bias, and confounding. Furthermore, we defined studies with a quality score of 60% or higher as studies with high quality [25].

The two reviewers (ToH and MB) independently extracted the information from the selected papers by using standardized and pre-tested data-extraction forms. The extracted information involved data on study population, diagnostic criteria, inclusion and exclusion criteria, setting, type of prognostic factors, duration of follow-up, outcomes, and data on associations. In case of disagreement, we reached consensus after discussion with a third reviewer (FvdL).

Data synthesis

We did not plan statistical pooling as we anticipated considerable heterogeneity. Therefore, a qualitative analysis (best evidence synthesis) was performed to summarize the value of the prognostic indicators. Furthermore, we considered the strength of evidence regarding a prognostic factor as strong, moderate, weak, or inconclusive depending on consistency of the findings and on quality of the study [26,27].

- strong: consistent findings (≥75% of the studies reporting on a factor showed the same direction of the association) in at least two high-quality studies
- moderate: consistent findings (≥75% of the studies reporting on a factor showed the same direction of the association) in one high-quality cohort and at least one low-quality study
- weak: findings of one high-quality cohort or consistent findings (≥75% of the studies reporting on a factor showed the same direction of the association) in at least three or more low-quality studies
- inconclusive: inconsistent findings irrespective of study quality, or less than three low-quality studies available

We only present prognostic factors which in at least one study showed a statistically significant association. Preferably, we derived the associations from the multivariate results. If only univariate results were presented in the original study, we used these univariate associations to determine the strength of evidence.

We present results of the studies on MUS, somatisation disorder, and hypochondriasis separately.

Results

We retrieved a total of 4867 publications from searches of the various electronic bibliographies (1673 PubMed, 933 PsycINFO, 1222 CINAHL, and 1039 EMBASE) (see Fig. 1). After screening the titles and abstracts, 68 abstracts seemed to fulfill the inclusion criteria. After assessing the full publication, 13 articles fulfilled all inclusion criteria

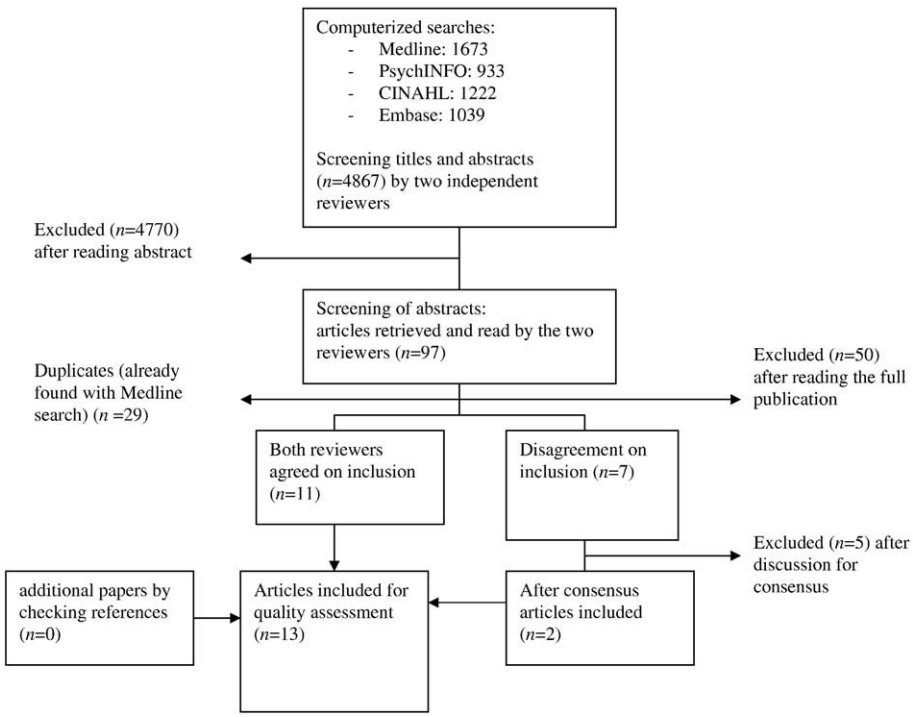

Fig. 1. Selection of studies.

Table 1
Results of the methodological quality assessment of prognostic cohort studies on MUS, abridged somatisation and hypochondriasis

	A	B	C	D	F	G	I	J	N	O	P	L	Q	R	E	H	K	M	S	T	U		
Quality criteria	Selection bias						Completeness of follow-up		Information bias			Confounding			Descriptive items							Quality score[a]	Score (%)
MUS																							
Kooiman et al., 2004 [30]	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	18	86.0
De Gucht et al., 2004 [29]	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	−	+	+	+	−	+	16	76.2
Speckens et al., 1996 [36]	+	+	+	+	?	?	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	16	76.2
Carson et al., 2003 [31]	+	+	+	+	?	+	−	+	+	+	+	−	+	−	−	−	+	+	+	+	−	14	66.6
Speckens et al., 1996 [37]	+	+	+	+	−	−	+	−	+	−	+	−	+	−	−	+	+	+	+	−	+	13	61.9
Henningsen et al., 2005 [28]	+	+	+	+	?	−	−	+	+	+	+	−	?	+	−	−	+	+	+	+	−	13	61.9
Abridged somatisation																							
Gureje and Simon, 1999 [40]	+	−	+	+	−	+	−	+	+	−	+	−	+	+	+	+	+	+	+	−	−	14	66.6
Hypochondriasis																							
Noyes et al., 1994 [35]	+	+	+	+	−	−	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	16	76.2
Barsky et al., 1998 [33]	+	+	+	+	?	?	−	+	+	−	+	−	+	+	−	+	+	+	+	+	−	14	66.7
Barsky et al., 2000 [32]	+	+	+	+	?	?	+	+	+	−	+	−	−	+	−	+	+	+	+	−	−	13	61.9
Barsky et al., 1993 [34]	+	−	+	?	−	−	−	−	+	+	+	−	+	−	−	+	+	+	+	+	+	12	57.1
Fernandez et al., 2005 [38]	+	+	+	+	−	−	+	−	+	−	+	−	+	−	−	−	+	+	+	+	−	12	57.1
Simon et al., 2001 [39]	+	−	+	+	−	+	?	+	+	−	+	−	−	−	−	+	+	+	+	+	−	12	57.1

[a] Total '+'.

Table 2
Summary of main study characteristics and course of MUS, abridged somatisation, and hypochondriasis

First author	Study quality (%)	Setting/country	Number enrolled in cohort	Criteria for diagnosis	Duration of follow-up [months (range)]	Loss to follow-up [*n*, (%)]	Gender (M/F) and age (years±S.D.) at baseline	Course
MUS								
Kooiman et al., 2004 [30]	81	General internal medicine outpatient clinic/The Netherlands	127	Judgment investigators on base of internist's final conclusion	14.1 (12.2–17.8)	0	43:84 40.2±12.7	62% improved; 38% not improved
De Gucht et al., 2004 [29]	76	Primary care practices/ The Netherlands	377	Judgment FP	6	59 (16.0)	103:274 43.5±12.2	53.1% decrease of symptoms; 33.6% increase of symptoms; 9.7% same [a]
Speckens et al., 1996 [36]	76	General medical outpatient clinic/ The Netherlands	81	Judgment investigators on base of medical records	15.2±4.0	0	28:53 39.4±10.7	30% recovered; 46% improved; 13% same; 11% worse
Carson et al., 2003 [31]	67	General neurology outpatients/UK	90	Judgment neurologist	8	24 (27.0)	24:42 [b] 42 [b]	46% improved; 41% same; 14% worse [c]
Speckens et al., 1996 [37]	62	General medical outpatient clinic/ The Netherlands	87	Judgment physician	11.6±0.8	5 (6.0)	Not given Not given	20% recovered; 51% improved; 18% same; 11% worse
Henningsen et al., 2005 [28]	62	Tertiary care clinics/ Germany	186	Judgment of 2 physicians	6	43 (23.0)	84:102 [b] 42.1±13.5 [b]	Not given
Abridged somatisation								
Gureje and Simon, 1999 [40]	67	Primary care/Europe, South America, US	1596	Diagnostic interview	12	525 (32.9)	Not given Not given	51.3% remitted; 48.7% unremitted
Hypochondriasis								
Noyes et al., 1994	76	Medicine clinic/US	50	Diagnostic interview	13.8 (12.6–20.3)	2 (4.0)	10:38 [b] 39.6±0.9 [b]	33% remitted; 67% unremitted
Barsky et al., 1998 [33]	67	Primary care clinic/US	C_1: 60 C_2: 60	Diagnostic interview	C_1: 64.7±6.8 C_2: 50.2±5.0	C_1: 13 (15.0) C_2: 22 (13.3)	22:63 [b] 53.5 [b]	36.5% remitted; 63.5% unremitted
Barsky et al., 2000 [32]	62	Primary care clinic/US	60	Diagnostic interview	50.2±5.0	22 (36.6)	11:27 [b] 48.0±15.2 [b]	34.2% remitted; 65.8% unremitted
Barsky et al., 1993 [34]	57	Primary care clinic/US	28	Diagnostic interview [d]	22.2 (12–35)	6 (21.4)	Not given Not given	Not given
Fernandez et al., 2005 [38]	57	Primary care health centre/Spain	25	Semi-structured interview and questionnaires [e]	11.3	4 (16.0)	6:19 40.1	52% remitted; 48% unremitted [e]
Simon et al., 2001 [39].	57	Primary care/Europe, South America, US	129	Diagnostic interview	12	Not given [f]	Not given Not given	84.5% remitted; 15.5% unremitted

C_1: cohort 1.
C_2: cohort 2.
[a] Number of MUS; 3.6 % missing.
[b] Baseline characteristics only calculated for patients who completed the follow-up period.
[c] According to the clinical global improvement scale.
[d] Transient hypochondriasis.
[e] Health anxiety.
[f] Loss to follow-up only calculated for the whole cohort of the World Health Organization's Psychological Problems in General Health Care (PPGHC) study [67].

Table 3
Prognostic factors

First author	Outcome measures	Prognostic factors	Direction of significant associations	Strength of association [a]
MUS				
Kooiman et al., 2004 [30]	(1) Symptom change (2) Change in general health perception (3) Medical consumption (4) Psychiatric pathology	(a) Alexithymia (b) Sociodemographic characteristics (c) Medical history (d) Mental problems (e) Illness behaviour (f) Symptom characteristics (g) Attribution	Symptom change – Longer duration of the symptom: absence of improvement – Higher number of physical symptoms: absence of improvement Change in general health perception (GHP) – Lower initial GHP at baseline: poor GHP at follow-up – Higher number of physical symptoms: poor GHP at follow-up – Less pain: poor GHP at follow-up	 β=0.01 (0.005), P<.05 β=0.05 (0.02), P<.05 β=−0.04 (0.01), P<.01 β=0.07 (0.03), P<.05 β=−0.03 (0.01), P<.05
De Gucht et al., 2004 [29]	(1) Changes in number of MUS (2) Symptom persistence or recurrence	(a) Neuroticism (b) Alexithymia (c) Negative or positive affective state (d) Sociodemographics	Number of MUS – Negative affect increase from T1 to T2: increase – Positive affect decrease from T1 to T2: increase Presence of a consistently high number of MUS – Female: increase – Consistently high negative affect: increase – Difficulty in identifying feelings (dimension of alexithymia): increase	 OR=1.78 (1.33 to 2.39) OR=0.71 (0.54 to 0.94) OR=2.29 (1.14 to 4.62) OR=2.77 (1.46 to 5.27) OR=1.08 (1.02 to 1.14)
Speckens et al., 1996 [36]	(1) Change in symptoms (2) Change in functional impairment	(a) Gender (b) Age (c) Number and duration of symptoms (d) Psychiatric disorders	Changes in symptoms – Female gender: absence of improvement – Higher number of symptoms: absence of improvement Change in functional impairment (FI): (b, 95% CI) – Higher FI at baseline: higher FI at follow-up – Higher age: higher FI at follow-up	 OR=2.7 (1.01 to 7.4) β=1.0 (0.1 to 1.9) β=0.30 (0.17 to 0.43) β=0.03 (0.01 to 0.05)
Carson et al., 2003 [31]	(1) Change in global clinical improvement	(a) Age (b) Gender (c) Health status (d) Mental state	Change in global clinical improvement [b] – Less physical function: absence improvement	 P<.02
Speckens et al., 1996 [37]	(1) Recovery of symptoms (2) Change in medical care utilization	(a) Hypochondriasis (questionnaire; WI) (b) Hypochondriasis (interview) (c) Illness attitude (d) Somatosensory amplification	Recovery of symptoms [b] – Higher scores on hypochondriasis questionnaire (WI): less recovery Change in medical care utilization (number of medical visits) [b] – Higher scores on illness behaviour subscale of the illness attitude scale: increase of number of medical visits	 β=− 0.89 (− 1.58 to − 0.20) β=0.31 (0.09 to 0.52)
Henningsen et al., 2005 [28]	(1) Affective and cognitive symptoms (2) Somatoform symptoms (3) Hypochondriasis (4) Quality of life	(a) Attribution	Affective and cognitive symptoms – Organic causal attribution: more depressive symptoms Quality of life – Organic causal attribution: less quality of life	 P<.03 P<.01
Abridged somatisation				
Gureje and Simon, 1999 [40]	(1) Persistence of abridged somatisation	(a) Gender (b) Self-rated poor health (c) Occupational disability (d) Physician-rated poor physical health (e) Depression (f) Generalized anxiety disorder (g) Age (h) Number of current symptoms at baseline	Persistence of abridged somatisation – Self-rated poor overall health: persistence – Moderate/severe occupational disability: persistence	 OR 1.82 (1.32 to 2.52) OR 1.55 (1.17 to 2.06)

Table 3 (*continued*)

First author	Outcome measures	Prognostic factors	Direction of significant associations	Strength of association [a]
Hypochondriasis				
Noyes et al., 1994	(1) Remission of hypochondriasis (2) Levels of hypochondriacal symptoms [c]	(a) Demographics (b) Health care utilization (c) Social adjustment (d) Overall functioning (e) Duration and scores of hypochondriacal symptoms (f) Health perception (g) Sensitivity to bodily sensations and environmental stimuli (h) Personality, neuroticism, extroversion (i) Comorbid depression or anxiety	Remission of hypochondriasis [b] – Lower scores of hypochondriacal symptoms on WI: remission – Lower scores of hypochondriacal symptoms on SSI: remission – Lower mean rating of hypochondriasis: remission – Shorter mean duration of illness: remission – Higher level of overall functioning: remission Level of hypochondriacal symptoms [c] – More unrealistic fear of illness: higher – Higher scores on SSI: higher – Higher somatosensory amplification: higher – Higher scores on somatisation (SCL-90): higher – Higher level of neuroticism: higher – Older age: higher – More social adjustment: higher	 $P<.05$ $P<.05$ $P<.05$ $P<.05$ $P<.05$ $r=0.4$; $P=.01$ $r=0.4$; $P=.01$ $r=0.39$; $P=.01$ $r=0.38$; $P=.02$ $r=0.36$; $P=.02$ $r=0.34$; $P=.02$ $r=0.34$; $P=.02$
Barsky et al., 1998 [33]	(1) Remission of hypochondriasis	(a) Hypochondriacal symptoms (WI and SSI) (b) Hypochondriacal somatic complaints (26-item SSI) (c) Symptom amplification (d) Functional status (e) Psychiatric comorbidity (f) Medical comorbidity	Remission of hypochondriasis – Decreases in hypochondriacal somatic complaints: remission	 $P<.05$
Barsky et al., 2000 [32]	(1) Remission of hypochondriasis	(a) Hypochondriacal somatic complaints (26-item SSI) (b) Somatosensory amplification (c) Normative beliefs about health and sickness	Remission of hypochondriasis – The 3-way interaction of health norms×hypochondriacal somatic complaints×amplification significantly increased the likelihood of a diagnosis of hypochondriasis at follow-up	 OR=0.98
Barsky et al., 1993 [34]	(1) Hypochondriacal symptoms (2) Somatisation (3) Disability	(a) Age (b) Gender (c) Personality disorder (d) Health status (e) Somatosensory amplification (f) Hypochondriacal symptoms (WI) (g) Hypochondriacal somatic complaints (SSI) (h) Intermediate activities of daily living	Number of hypochondriacal symptoms – Higher somatosensory amplification: more hypochondriacal symptoms	 P not given
Fernandez et al., 2005 [38]	(1) Persistent health anxiety	(a) Depression/anxiety (b) Negative affectivity (c) Somatic discomfort (d) Personal and family experiences related to illness throughout childhood (e) Current stress and illness (f) Sociodemographics (g) Satisfaction with medical attention (h) Evaluation of state of health (i) Degree of health anxiety	Persistent health anxiety [b] – Less positive medical self-evaluation of health problems: persistence – Greater degree of self-judged health anxiety: persistence	 $P=.031$ $P=.049$
Simon et al., 2001 [39]	(1) Persistence of hypochondriasis	(a) Anxiety (b) Depressive disorder	No significant association found	

WI: Whitely Index; SSI: Somatic Symptom Inventory; SCL-90: Symptom Checklist-90.

[a] Adjusted estimates and 95% CI.

[b] Only univariate results available (crude estimates and 95% CI, significant differences or associations).

[c] The measure of hypochondriacal symptoms at follow-up was the sum of the Whitely Index×5.6+the Somatic Symptom Inventory.

and were included in our review [28–40]. Major reasons for excluding papers were focus not on patients with medically unexplained symptoms (n=30) and no study of prognostic factors (n=14). The reference lists of the retrieved papers did not reveal any relevant publication. Six studies reported on MUS [28–31,36,37], six studies on hypochondriasis [32–35,38,39], and one study on abridged somatisation [40]. The abridged definition of somatisation required the presence of four symptoms in males and six symptoms in females [41]. We did not find any prospective cohort studies on *DSM-IV* somatoform disorders.

The interobserver agreement for inclusion between the two reviewers (ToH, MB) was κ=0.73 (95% CI: 0.59–0.87). We considered the strength of agreement to be 'good' [42].

Study characteristics

We found six studies on MUS. Table 1 gives the data of the quality assessment of the included studies. The quality score of MUS publications ranged from 62% to 86%. As none of the included studies described a treatment subsequent to inclusion in the study cohort (Item L), we cannot decide on whether the natural course was studied or course during treatment (as usual). Loss to follow-up ranged from 0% to 27%.

We found one prospective cohort study on abridged somatisation. The quality of this publication scored 67%.

We included six studies on hypochondriasis. The methodological quality score of hypochondriasis publications ranged from 57% to 76% (see Table 1). As in the MUS studies, in these six hypochondriasis studies, application of treatments was not described. So whether the natural course or course during treatment was studied cannot be concluded. Selection bias and confounding were present in all studies and in four of the six studies information bias was presented [32,33,38,39] (see Table 1). Loss to follow-up ranged from 4% to 36.6%.

A summary of the study characteristics is presented in Table 2, including population, setting, diagnostic criteria, follow-up, and baseline characteristics.

Four of the six studies on MUS are performed in the Netherlands. Studies reporting on MUS defined MUS as symptoms that could not be attributed to a clear organic cause according to the physician's judgment after a thorough physical examination including laboratory tests. So, physician's judgment was often the most important diagnostic instrument.

In these six MUS studies, we found high levels of heterogeneity regarding clinical setting (primary care, secondary care, and tertiary care), numbers enrolled in the cohort (80 to 377 patients), duration of follow-up (6 to 15 months), and loss to follow-up (0 to 27%). Only two studies reported on the duration of symptoms at baseline [28,36]. Speckens et al. [36] reported a median duration of symptoms of 7.8 months (range 0–168), whereas Henningsen et al. [28] reported a mean duration of 70±94 months (median 26).

The study on abridged somatisation was performed in primary care from 15 sites in 14 countries and enrolled 1596 patients into the cohort. Abridged somatisation was diagnosed according to the Somatic Symptoms Index (SSI). Duration of symptoms at inclusion was not reported.

All studies on hypochondriasis used a formal diagnostic interview to diagnose patients with hypochondriasis as stated in the *DSM-III-R* (see Table 2). Fernandez et al. [38] included patients with health anxiety. These patients share many characteristics with patients suffering from hypochondriasis [38]. Despite the use of formal diagnostic interviews, there was considerable heterogeneity in the six included studies. Duration of follow-up (1 to 5 years), numbers enrolled in the cohort (50 to 129 patients), and loss to follow-up (4% to 37%) vary considerably between the included studies. Only two studies reported on duration of symptoms at baseline. Noyes et al. [35] included patients with a median duration of symptoms of 19 (range 2–144) months. Fernandez et al. [38] reported that worries on health started more than 5 years ago in 36% of the patients, whereas in 12% of the patients these worries started in the last 6 months.

Course of MUS, somatisation disorder, and hypochondriasis

Five out of six articles on MUS reported on the course of the symptoms (see Table 2). Based on prevalence, the typical MUS patient in our review is female, between 35 and 45 years old, and consulted a primary care practice or secondary care outpatient clinic. Irrespective of the clinical setting, the majority of the patients with MUS (50% to 75%) improve during follow-up. However, about 10% to 30% of the patients deteriorate.

Five out of six studies on hypochondriasis reported on the course of hypochondriasis. Based on prevalence, the typical hypochondriasis patient is again female and between 35 and 45 years old. Fifty percent to 70% of the patients with hypochondriasis did not recover. Only Simon et al. [39] found a recovery rate in hypochondriasis patients of 85%.

The only study on somatisation disorder studied a modified concept [40]. Recovery rates were comparable with the data found in studies on MUS patients.

Prognostic factors of MUS, somatisation disorder, and hypochondriasis

In Table 3, a summary of outcomes measures, prognostic factors, and (strength of) significant associations is given. Apart from the high heterogeneity in study characteristics, we also found considerable heterogeneity in prognostic factors and outcome measures in the 13 studies included in this review.

Table 4
Strength of evidence of prognostic factors with a significant influence on outcome in multivariate analysis

Prognostic factor	Outcome	QS>60%	QS<60%	Strength of evidence
MUS				
Affective state/depressivity	Symptom change	1/2 (50%)	–	Inconclusive
Female gender	Symptom change	2/3 (66%)	–	Inconclusive
Alexithymia	Symptom change	1/2 (50%)	–	Inconclusive
Symptom duration	Symptom change	1/2 (50%)	–	Inconclusive
Number of symptoms	Symptom change	2/2 (100%)	–	Strong
Hypochondriasis questionnaire (WI)	Symptom change	1/3 (33%)[a]	–	Inconclusive
Initial GHP	Change in general health perception	1/1 (100%)	–	Weak
Number of physical symptoms	Change in general health perception	1/1 (100%)	–	Weak
Pain	Change in general health perception	1/1 (100%)	–	Weak
Physical function[b]	Change in global clinical improvement	1/1 (100%)	–	Weak
Age	Difference in functional impairment	1/1 (100%)	–	Weak
Illness behaviour subscale of IAS[b]	Change in medical care utilization	1/1 (100%)	–	Weak
Attribution	Quality of life	–	1/1 (100%)	Inconclusive
Abridged somatisation				
Self-rated overall health	Persistence of abridged somatisation	1/1 (100%)	–	Weak
Occupational disability	Persistence of abridged somatisation	1/1 (100%)	–	Weak
Hypochondriasis				
Health norms×somatisation×amplification[c]	Remission of hypochondriasis	1/1 (100%)	–	Weak
Hypochondriacal somatic complaints (SSI)	Remission of hypochondriasis	2/2 (100%)[d]	–	Strong
Hypochondriacal symptoms (WI)[b]	Remission of hypochondriasis	1/1 (100%)	–	Weak
Rating of hypochondriasis[b]	Remission of hypochondriasis	1/1 (100%)	–	Weak
Duration of illness[b]	Remission of hypochondriasis	1/1 (100%)	–	Weak
Level of overall functioning[b]	Remission of hypochondriasis	1/1 (100%)	–	Weak
Unrealistic fear of illness	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Hypochondriacal symptoms (SSI)	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Somatosensory amplification	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Somatisation (SCL-90)	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Neuroticism	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Age	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Social adjustment	Hypochondriacal symptom level	1/1 (100%)	–	Weak
Somatosensory amplification	Number hypochondriacal symptoms	–	1/1 (100%)	Inconclusive
Self-evaluation of health problems[b]	Change in health anxiety	–	1/1 (100%)	Inconclusive
Degree of self-judged health anxiety[b]	Change in health anxiety	–	1/1 (100%)	Inconclusive

Only factors are presented which scored significant associations in at least one study.
QS: Quality score; IAS: Illness Attitude Scale.
[a] Significant association only in one study with univariate analysis.
[b] Only univariate analysis available.
[c] Only the three-way interaction significantly improved the model and increased the likelihood of a diagnosis of hypochondriasis at follow-up.
[d] Significant association in one study with multivariate analysis and in one study with univariate analysis.

Four of the six publications on MUS studied potential prognostic factors on the outcome 'symptom change' [29,30,36,37].

There is some evidence that the number of symptoms at baseline predicts the course of MUS. (see Table 4). Moreover, it seems that the more serious the condition at baseline, the more unfavourable the prognosis. This is represented by the factors general health perception (GHP), degree of pain, physical functioning, and illness behaviour. It is unclear whether female gender predicts an unfavourable course of MUS as two studies found that gender was of prognostic significance, whereas one study found that gender was not of prognostic significance [31]. Studies on comorbid mental health problems such as affective state and alexithymia showed conflicting results [29,30,36].

We found weak evidence that poor self-evaluation of overall health and for occupational disability at baseline predicts persistence of abridged somatisation [40].

Potential prognostic factors on recovery of hypochondriasis were studied in four publications (see Table 3) [32,33,35,39]. We found some evidence for the number of somatic complaints on the Somatic Symptom Inventory (SSI) at baseline predicting recovery of hypochondriasis. A higher score predicts persistence of hypochondriasis (Table 4) [33,35]. Furthermore, we found weak evidence for the prognostic value on the course of hypochondriasis of symptoms scores on the Whitley Index, rate of severity of hypochondriasis, duration, level of functioning, and degree of unrealistic fears of illness. Again, it looks like that the more serious the condition at baseline, the more

unfavourable the outcome (i.e., persistence of hypochondriasis). Psychiatric comorbidity seems not to influence the course of hypochondriasis [33,35,38,39], whereas somatosensory amplification seemed to influence the outcome of hypochondriasis in two studies [34,35].

Discussion

Main results

Although a lot of research has been done on the epidemiology of and interventions for medically unexplained symptoms, we are not aware of a systematic review of the literature that focuses on the course and the prognosis of medically unexplained symptoms. Creed and Barsky [7] performed a systematic review of the epidemiology of somatisation disorder and hypochondriasis to examine the characteristics and associated features of these disorders. However, they did not systematically search and study prognostic factors [7]. So, this is the first systematic review which systematically searched for studies on prognostic factors in this area.

Generally, the included studies were of good quality. However, the heterogeneity between those included studies regarding clinical setting, numbers enrolled in the cohort, duration of follow-up, loss to follow-up, prognostic factors, and outcome measures used is considerable. This limits direct comparability of the studies and makes it difficult to draw reliable conclusions.

The studies on MUS and abridged somatisation showed improvement rates of 50% or more. This is better than we expected. However, 10% to 30% of patients with MUS deteriorate. Given the large numbers of patients presenting with MUS in primary and secondary care, deterioration of one third of these patients still means that large numbers of patients with MUS are going to get worse. The studies on hypochondriasis showed a less optimistic picture: the majority of these patients (50% to 70%) do not recover during follow-up. This might be due to the definition of hypochondriasis which requires patients to have symptoms for 6 months or more.

We did not find any prospective study on course or prognostic factors in patients with *DSM-IV* somatoform disorders. As the evidence for the number of symptoms at baseline in MUS as a prognostic factor originate from only two of the included MUS study, we conclude that there is some evidence that the number of symptoms at baseline predicts the course of MUS. In the studies on hypochondriasis, we found some evidence that the somatic symptom score on the SSI at baseline predicts the course of hypochondriasis. Furthermore, the condition of patients with MUS at baseline, represented by health perception and physical functioning, and the condition of patients with hypochondriasis at baseline, represented by rating of severity, physical functioning, and duration of illness, showed a weak association with the outcome of MUS and hypochondriasis. So, we conclude that there is some evidence that the seriousness of the conditions of patients with MUS or hypochondriasis at baseline might be of prognostic significance.

We found only weak evidence for many other prognostic factors. Evidence on gender to be of prognostic significance was inconclusive. Remarkably, we found no evidence to support the influence of psychiatric comorbidity and personality traits on the course of MUS, abridged somatisation, and hypochondriasis.

Comparison with the literature

Although only a minority of the MUS presented during consultation result in a chronic condition, patients with MUS are problematic in health care [4]. Physicians perceive these patients as difficult and demanding [43,44]. They also believe that patients with MUS increase health care costs due to sickness absence and service use and that they are at risk for unnecessary diagnostic procedures. Physicians express the need to prevent somatic fixation in these patients [45–47]. However, we found that the prognosis of MUS in primary and secondary care is more favourable than expected, as the majority of the patients with MUS improve. A possible explanation for this finding is that improvement of symptoms is partly caused by regression to the mean because symptoms are on their worst when selecting patients during primary or secondary care clinic visits.

However, our finding that the majority of the patients with hypochondriasis do not recover is supported by the literature in which hypochondriasis is considered to be a chronic condition [3,48,49]. Although, according to the literature, spontaneous recovery of hypochondriasis is rare, we found recovery rates of 33% to 50%. A possible explanation for this finding might be the procedure as required for inclusion in the study cohorts. This procedure is an extensive clinical assessment consisting of diagnostic interviews and additional testing and might in itself be of therapeutic importance [50,51].

Given the many factors hypothesized to be prognostic for a chronic course of MUS, somatisation disorder, and hypochondriasis, there is not much evidence on these factors. Although personality traits, including neuroticism and alexithymia [52,53], and psychiatric comorbidity, including anxiety and depression [54–56], have been demonstrated to be associated with MUS and hypochondriasis, only a limited number of studies have examined their prognostic value. In this review, we did not find evidence for their prognostic value [29,30,33,35–39]. However, in well-defined medically unexplained syndromes such as chronic fatigue syndrome and irritable bowel syndrome the evidence on prognostic factors is much stronger [57–61]. Cairns and Hotopf [57] found that less fatigue severity at baseline, a sense of control over symptoms, and not attributing illness to a physical cause were associated with a good outcome. Their findings of the prognostic significance of the fatigue severity at baseline are in line with our findings.

Strengths and limitations

In this systematic review, we used an extensive search strategy to identify relevant studies. We added rigor to our study by pre-testing the search strategy on publications about MUS in our own database and by searching all relevant databases without language restriction. Moreover, we had good interobserver agreement for inclusion and exclusion. Finally, we independently extracted data and assessed the quality of included studies with a validated checklist.

Because the quality of the individual study influences outcomes, we presented our results together with a quality score of each study. So, we visualize the susceptibility of each study for bias. Currently, no standardized method is available to assess the quality of prognostic studies. Therefore, we used a checklist of predefined criteria which has been used in previous prognostic reviews [20,21].

The median number of participants enrolled in the cohorts of the included studies in this review is 87. Only one study on MUS, one study on abridged somatisation, and none of the studies on hypochondriasis enrolled more than 200 patients into the cohort [29,40]. These low numbers of participants in the cohorts limit the strength of the evidence concerning outcome and prognostic factors.

Only a minority of the included studies presented sufficient data on the duration of symptoms at baseline. Therefore, it is not clear whether the study patients were all included at a similar point in the course of their disease. Studies reporting duration of symptoms at baseline showed a considerable range of duration of symptoms. This also limits the interpretation of our results.

Another limitation of this review is the absence of a detailed description of treatments during follow-up. The results of our study apply to the course of MUS, hypochondriasis, and somatisation disorder in the medical system. We assume that during the studies in all patients some kind of treatment has been applied, although no study reported on this.

As statistical pooling was not possible because of the high heterogeneity of study populations, prognostic factors, and outcome measures among included studies, we performed a best-evidence synthesis. Although such a qualitative analysis is not as objective as a meta-analysis, we were able to summarize the value of prognostic indicators which takes the methodological quality into account [62].

Implications for further research and clinical practice

The pessimistic views of GPs and their worries about the development of somatic fixation in patients with MUS and abridged somatisation might not always be justified as the majority of these patients generally have a favourable prognosis. However, the majority of the patients with hypochondriasis do not recover, suggesting that hypochondriasis is a more severe condition.

Establishing the number of somatic symptoms and seriousness of the condition in patients with MUS or hypochondriasis during the first consultations might help GPs to value the risk of persistence and may guide GPs whether to offer only reassurance about the favourable prognosis or, for the high-risk patients, a more intensive approach such as reattribution. However, due to its heterogeneity, the data collated in this systematic review on prognostic factors are inadequate to identify predictors of the course of MUS, somatisation disorder, and hypochondriasis. Therefore, it is difficult to advise clinicians on how to distinguish between patients with low and high risks of persistence.

Although it is widely accepted that personality traits and comorbid depression and anxiety are associated with MUS, somatisation disorder, and hypochondriasis, studies examining their prognostic value show conflicting results. As a consequence of the paucity of current research, there is a need for more well-conducted prospective cohort studies with a reasonable number of patients (>200 patients), in which assessment of treatments during follow-up and inclusion of patients at a similar point in the course of their disease are important topics.

Although we know for long that the doctor–patient relationship affects the outcome of consultations and can be therapeutic, none of the included studies took the doctor–patient relationship into account [63–65]. The more nonspecific aspects of consultation such as described in the patient-centred clinical method need attention in future research [66].

Acknowledgments

All authors participated in the research process (study design: ToH, PL, FvdL, CvW; data collection: ToH, MB; data analysis and interpretation: ToH, MB, FvdL, PL, AS. ToH, MB, and PL drafted the manuscript and all authors helped with revisions to the manuscript). ToH and MB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version.

Appendix A. Search strategy

(somatoform disorder [mesh] OR somatization [tw] OR somatisation [tw] OR hypochondriasis [mesh] OR neurasthenia [mesh] OR conversion disorder [mesh] OR somatoform disorder* [tw] OR hypochondriasis [tw] OR neurasthen* [tw] OR conversion disorder* [tw] OR psychophysiological disorder [Mesh] OR psychosomatic medicine [Mesh] OR psychophysiological disorder* [tw] OR psychosomat* [tw] OR psychosomatic medicine [tw] OR functional somatic sympt* [tw] OR functional somatic syndrom* [tw] OR functional syndrom* [tw] OR unexplained sympt* [tw] OR medically unexplained [tw] OR

unexplained medical sympt* [tw] OR psychogen* [tw] OR non-organ* [tw] OR non-specific complain* [tw] OR non-specific sympt* [tw]) **AND** (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH: noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]) **AND** (((Prospective studies [mesh] OR cohort studies [mesh] OR follow-up studies [mesh] OR observational stud* [tw] OR prospective stud* [tw] OR cohort stud* [tw] OR follow-up stud* [tw])) *OR* ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh: noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])))

Appendix B. Criteria list for assessing the methodological quality of prognostic cohort studies on chronic medically unexplained symptoms

Criteria	Score
Study population	
A. Description of inception cohort	+/−/?
B. Description of study population	+/−/?
C. Description of relevant inclusion and exclusion criteria	+/−/?
D. Definition of chronic functional somatic symptoms	+/−/?
E. Number of subject in study population ≥200	+/−/?
Response	
F. Response rate ≥75%	+/−/?
G. Information about nonresponders vs. responders	+/−/?
Follow-up (extend and length)	
H. Follow-up of at least 12 months	+/−/?
I. Loss to follow-up <20%	+/−/?
J. Information about completers vs. those lost to follow-up	+/−/?
K. Prospective data collection	+/−/?
Treatment	
L. Description of possible treatment in cohort	+/−/?
Outcome	
M. Clinically relevant outcome measures	+/−/?
N. Standardized assessment of symptom outcome	+/−/?
O. Standardized assessment of functional outcome	+/−/?
Prognostic factors	
P. Standardized assessment of potential prognostic factors	+/−/?
Analysis	
Q. Appropriate univariate crude estimates	+/−/?
R. Appropriate multivariate analysis techniques	+/−/?
Data presentation	
S. Frequencies of most important outcome measures presented	+/−/?
T. Frequencies of most important prognostic factors presented	+/−/?
U. Influence of prognostic factors presented	+/−/?

+, positive (design or conduct adequate); −, negative (design or conduct inadequate); ?, unclear (insufficient information).

Appendix C. Explanation of the criteria of the checklist for methodological quality

A. Description of inception cohort

Positive if it is described in what setting the subjects were recruited (i.e., general population, patients attending the general practitioner, inpatient or outpatient setting).

B. Description of study population

Positive if it is described which subjects from the inception cohort are recruited and if age and sex are described.

C. Description of relevant inclusion and exclusion criteria

Positive if it is described how subjects were identified with chronic functional somatic symptoms (CFSS) or somatization.

+=CFSS or somatization diagnosed by the general practitioner or standardized diagnostic interview

−=CFSS or somatization diagnosed by a (standardized) self-administered symptom checklist

?=not clear

D. Definition of chronic functional somatic symptoms

Positive if the definition is described of CFSS or somatization.

E. Number of subjects in study population ≥200

Positive if the number of subjects with CFSS or somatization in the study population was at least 200 at baseline.

F. Response rate ≥75%

Positive if response rate is at least 75%. Response rate: the number of patients in the study population, divided by the number of subjects in the inception cohort.

G. Information about nonresponders vs. responders

Positive if demographic or clinical information (such as age and sex) was presented for responders and non-responders, or if there was no selective response, or no nonresponse.

H. Follow-up of at least 12 months

Positive if the follow-up period was at least 12 months.

I. Loss to follow-up <20%

Positive if total number of patients with CFSS or somatization was at least 80% at the end of follow-up compared to the number of participants with CFSS or somatization at baseline. Loss to follow-up: the number of patients in the study population at baseline minus the number of patients at the main health status measurement for the main outcome measure at the end of follow-up, divided by the number of patients in the study population at baseline.

J. Information about completers vs. those lost to follow-up/dropouts

Positive if demographic or clinical information (such as age and sex, disease characteristics, and other potential prognostic predictors) was presented for completers with CFSS or somatization and those lost to follow-up at the main moment of outcome measurement, or if there was or no selective loss to follow-up, or no loss to follow-up.

K. Prospective data collection

Positive if main outcome measures on potential prognostic predictors were collected prospectively.

L. Description of possible treatment in cohort

Positive if treatment subsequent to inclusion in cohort is fully described or standardized. Also positive if no treatment is given.

+=treatment/multivariate correction for treatment in analysis, or no treatment given

−=different treatment regimens, not clear how outcome is influenced by it

?=not clear if any treatment is given

M. Clinically relevant outcome measures

Positive if at least one of the following outcome measures is presented: CFSS/somatization diagnosis, symptoms, remission or recurrence, functional status, social functioning, lost days of work, quality of life, impairment, mortality

N. Standardized assessment of symptom outcome

Positive if standardized questionnaires or objective outcome measurements of at least one of the following three outcome measures were used for each follow-up measurement:

a. CFSS/somatization diagnosis
b. Symptoms
c. Remission or recurrence

O. Standardized assessment of functional outcome

Positive if standardized questionnaires or objective outcome measurements of at least one of the following six outcome measures were used for each follow-up measurement:

a. functional status
b. social functioning
c. lost days of work
d. quality of life
e. impairment
f. mortality

P. Standardized assessment of potential prognostic factors

Positive if standardized questionnaires or objective measurements were used at baseline of at least four of the following 18 potential prognostic factors

a. sex
b. age
c. marital status
d. family history of CFSS/somatization
e. race
f. social economic status (SES)
g. education level
h. number of episodes of CFSS/somatization
i. sick leave
j. functional impairment
k. comorbidity (i.e., anxiety disorder or chronic disease)
l. duration of symptoms
m. social support
n. stressful life events
o. difficult doctor-patient relationship
p. coping strategy
q. perception of symptoms (i.e., illness attitude, somatosensory amplification)
r. personality traits

Q. Appropriate univariate crude estimates

Positive if separate univariate (repeated measures) analysis of variance was calculated for each dependent measure.

R. Appropriate multivariate analysis techniques

Positive if multivariate (repeated measures) analysis of variance was calculated for changes among the dependent measures occurring during the follow-up interval.

S. Frequencies of most important outcome measures presented

Positive if frequency, percentage or mean, median (interquartile range), and standard deviation/confidence intervals are reported of the most important outcome measures

T. Frequencies of most important prognostic factors presented

Positive if:

a. frequency of percentage is reported, or
b. mean and standard deviation or standard error are reported, or
c. median and interquartile range are reported, or
d. if the influence of each separate factor is reported

U. Influence of prognostic factors presented

Positive if the influence of each separate prognostic factor on the natural course of CFSS or somatization is presented.

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