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Prevalence of medically unexplained symptoms in adults who are high users of healthcare services and magnitude of associated costs: a systematic review

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ABSTRACT

Introduction Medically unexplained symptoms (MUS) is a common clinical syndrome in primary and secondary healthcare service. Outcomes for patients with persistent MUS include increased disability, poorer quality of life and higher healthcare costs. The aim of this systematic review was to determine the prevalence of MUS in patients who are high users of healthcare or high-cost patients in comparison with routine users and the magnitude of associated costs.

Design A systematic review of the available literature.

Data sources and eligibility criteria The following electronic databases were systematically searched without language restriction from inception to June 2018 and updated on 22 October 2021: MEDLINE, PsycINFO, EMBASE, CINAHL and PROSPERO. Inclusion criteria included studies investigating adults aged ≥18 years, who were high healthcare users or accrued high healthcare costs, in which the prevalence and/or associated costs of MUS was quantified. Two reviewers independently extracted information on study characteristics, exposure and outcomes.

Results From 5622 identified publications, 25 studies from 9 countries involving 31 650 patients were selected for inclusion. Due to high risk of bias in many studies and heterogeneity between studies, results are described narratively. There were wide variations in prevalence estimates for MUS in high users of healthcare (2.9%–76%), but MUS was more prevalent in high use groups compared with low use groups in all but one of the 12 studies that included a comparator group. Only three studies investigated healthcare costs associated with MUS, and all three reported greater healthcare costs associated with MUS.

Conclusion MUS has been found to be more prevalent in high use healthcare populations than comparator groups, but the magnitude of difference is difficult to estimate due to considerable heterogeneity between studies and potential for bias. Future studies should prioritise a standardised approach to this research area, with agreed definitions of MUS and high healthcare use.

PROSPERO registration number CRD42018100388.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To reduce bias, this review was not restricted to the English language or publication date.
⇒ A wide range of medical databases and study types was used to identify potential papers for inclusion.
⇒ A broad search strategy with a wide spectrum of search terms, including healthcare cost/utilisation, frequent attenders, MUS and healthcare settings, was used.
⇒ Two reviewers conducted study selection, data extraction and quality assessment independently.
⇒ A meta-analysis of the results was not possible due to the high risk of bias among studies and methodological heterogeneity between them, thus a narrative summary of the outcome of the selected studies was presented in the final review.

BACKGROUND

Medically unexplained symptoms (MUS) is a general term that refers to the presence of persistent bodily symptoms without an obvious cause, or that cannot be explained by recognised pathological mechanisms.[1] It covers a wide spectrum of complaints that can vary in nature, site, severity and chronicity. In some people, MUS presents as mild discomfort that does not significantly impact functioning; at the more severe end, individuals can experience clinically severe symptoms that cause disability and functional impairment, particularly if appropriate treatment is not sought.[2] The term 'MUS' has received criticism as it suggests a classification based on exclusion and a newer term persistent physical symptoms is preferred by patient groups.[3] MUS is a clinical construct, whereby a clinician decides whether symptoms have an organic cause or not based on clinical history, examination findings and investigation results. There are difficulties translating this to research settings, and broad definitions have been needed historically to

capture the breadth of presentations seen in clinical practice. This requirement for an exclusion of organic disease has been removed from Diagnostic and Statistical Manual of Mental Disorders V (DSM-V)[4] and in the 'somatic symptom and related disorders' section, there is a focus on a person's reaction to physical symptoms rather than the nature of the symptoms themselves. However, as most of the studies included in this review use the term MUS, and predate the publication of DSM-V, we have retained use of the term for the sake of clarity. Within the use of the term MUS, we include all relevant diagnostic terms including the somatoform disorders.

In recent years, MUS has received more attention and it is now routinely referred to in the literature.[5] MUS is highly prevalent across all healthcare settings and accounts for approximately 45% of all general practice consultations and 20% of new consultations in primary care.[6 7] MUS is also common in secondary care,[8] and accounts for 20%–25% of all frequent attenders in medical clinics.[9 10]

MUS is associated with a significant economic burden for healthcare systems. Patients with MUS are routinely referred for multiple assessments and investigations to little benefit and have longer doctor visits compared with other patients.[11 12] They incur more sick leave and have significantly higher rates of unemployment.[13–15] MUS accounts for approximately 10% of the NHS annual expenditure in adults of working age in England. The annual cost attributable to MUS due to lost productivity and decreased quality of life is over £14 billion to the UK economy.[16] However, there is no satisfactory review of the available literature to support such estimations.

The overall purpose of this systematic review is to determine the prevalence of MUS in patients who are high users of healthcare and/or who accrue high healthcare costs and the magnitude of healthcare or associated costs.

Aims

This systematic review aims to:

- Determine the prevalence of MUS in adults aged≥18 years who are high users of healthcare or 'high-cost' patients (those who accrue high healthcare costs), in comparison with routine users of healthcare.
- Determine the magnitude of the cost of use of healthcare associated with the presence of MUS among adults who are high users of healthcare.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement guidelines (online supplemental file 1).[17] The review protocol is registered in the PROSPERO database. Assuming heterogeneity between studies, we planned to conduct a random effect meta-analysis with and without low-quality studies. The review protocol has been published elsewhere.[18]

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study. The research question of this review was informed by the lack of relevant literature examining the prevalence of patients with MUS who are high users of healthcare or who accrue high healthcare costs. Therefore, patients and the public were not involved in defining the research question or outcome measures.

Eligibility criteria

This review-included studies where cases are adults aged 18 years or over, who are high users of healthcare services or have high general healthcare costs and MUS. We included studies which described 'patients who accrue high healthcare costs', 'high users', 'distressed high users or users of care', 'frequent attenders in primary care and secondary care' and 'frequent attenders at the emergency department'. In all studies, a recognised measure of the presence of MUS was required. This included application of any of the following: a standardised research interview (the Structured Clinical Interview for Mental Disorders)[19 20] to generate a diagnosis of a somatoform disorder according to DSM-III,[21] DSM-IV,[22] International Classification of Diseases (ICD-10 F45 diagnoses),[23] structured clinical interview (SCID) for DSM-IV and abridged criteria for somatoform disorder,[24] the Diagnostic Criteria for Psychosomatic Research (DCPR),[25] General Health Questionnaire-28 (GHQ-28) somatisation subscale,[26] Patient Health Questionnaire-15 (PHQ-15),[27] Symptom Checklist-90-Revised (SCL-90-R),[28] the schedules for clinical assessment in neuropsychiatry (SCAN)[29] and clinical assessment for MUS in secondary care. Studies focusing on mental health services, or specific medical subspecialties, for example, oncology or obstetrics, were excluded. Observational studies, including retrospective and prospective cohort studies, case–control and cross-sectional studies were considered for this review. Single case studies and randomised controlled trials were excluded.

Search strategy

A comprehensive search strategy was developed to retrieve articles relevant to the principal aims of this review. The following electronic databases were systematically searched without language restriction from inception to June 2018 and updated on 22 October 2021: MEDLINE, PsycINFO, EMBASE, CINAHL and PROSPERO. The Cochrane library was also included in view of the significant proportion of non-observational studies currently published in the database. Ongoing studies, scientific literature and abstract proceedings were identified by searching the Cochrane Database of Systematic Reviews, Royal College of Psychiatrists, American Psychiatrists Association and Zetoc. Grey literature databases such as Grey Literature Report, OpenGrey, PubliCat and ScienceDaily.com were also examined. Open access theses and dissertations were retrieved from the ProQuest

Table 1 Review eligibility criteria checklist

Study design	Cohort studies (retrospective and prospective) Case–control and nested case–control studies Cross-sectional studies
Study characteristics	Full articles Reference lists of any recent review article Eligible manuscript identified by database search
Participants	Adult aged ≥18 years High user of healthcare Accrue high healthcare costs Presence of MUS
Comparator	Non-high cost and non-high users of healthcare
Outcome	Prevalence of MUS Patient characteristics and context associated with high service usage/costs among patients with MUS Magnitude of cost or use of healthcare associated with the presence of MUS

MUS, medically unexplained symptoms.

Dissertation Thesis Database and thesis.com. The reference lists of any recent review articles and from any other eligible manuscript identified by the above search were hand-searched. The Science Citation Index was used to scan and track study titles. Search strategies for each database are shown in online supplemental file 2.

Study selection

All records retrieved in the database search were imported into the literature management software EndNote to facilitate the management of references. Two reviewers (FJ and OL) independently reviewed the studies identified by the search strategy in two phases. Retrieved titles and abstracts were initially reviewed to identify eligibility for full-text screening. The full texts were then read to determine suitability for inclusion in the review. This was achieved by referring to an inclusion criteria checklist designed a priori (table 1) based on study eligibility criteria. Any discrepancies or differences in opinion were resolved by consensus.

Data extraction

Prior to data extraction, a standardised data extraction form was developed (online supplemental file 3) based on the Hayden *et al*'s framework.[30] This was developed iteratively with a focus on population, comparator, outcome and study design, then pilot-tested on known papers independently by two reviewers (FJ and OL). Following initial familiarisation with the included studies, two reviewers (FJ and DR) independently extracted the following information using the form: study design, study details (author(s), publication year and country), recruitment setting (eg, primary care), sample size, diagnostic and screening method used to diagnose MUS, sample characteristics (age and gender), reported prevalence of MUS, magnitude of costs associated with MUS and service use (eg, frequency of attendance). Data extraction using the same method was then completed by two other reviewers (AB and EG) to minimise the likelihood of missed or misinterpreted information. Any discrepancies were resolved by discussion and revisiting the relevant study. Descriptive data extracted from included papers were summarised in a Microsoft Excel spreadsheet.

Quality assessment

Two reviewers (FJ and DR) completed a quality assessment of each included article independently to reduce bias. The quality assessment focused on sampling strategy, methods used to establish exposure and outcome, and analytical method employed. All selected articles were assessed using a modified form adapted from the Ottawa-Newcastle Scale[31] assessing the quality of cohort, case–control and cross-sectional studies. The stages and domains of this modified tool are shown in online supplemental file 4. Quality assessment using the same method was then completed by two other reviewers (AB and EG) to minimise the likelihood of personal judgements and subjectivity influencing reported study quality. Any difference in opinion was resolved by further discussion and/or by involving a third reviewer. Risk of bias was presented according to the Cochrane Collaboration recommendations.[32] Risk of bias was not displayed as a composite score; instead, an outcome of 'high risk', 'low risk' or 'unclear' was provided for each domain of the tool. A sensitivity analysis may be conducted to assess the effect of including or excluding poor quality studies on the main findings.

Statistical analysis

Estimates of MUS prevalence were considered separately for age, gender, ethnicity and definition of MUS, where applicable. Prevalence estimates were either reported as frequency (%), mean (SD) or OR with 95% CI between groups. Level of heterogeneity between study data was explored. We planned to quantify heterogeneity using the Cochrane Q-test and the I^2-statistical test with 95% CI if appropriate. The magnitude of healthcare utilisation and costs defined by high users or patients who accrue high healthcare costs were extracted for each study. Where reported, differences between the cost or use of healthcare associated with the presence of MUS were recorded. Standardised mean difference with accompanying

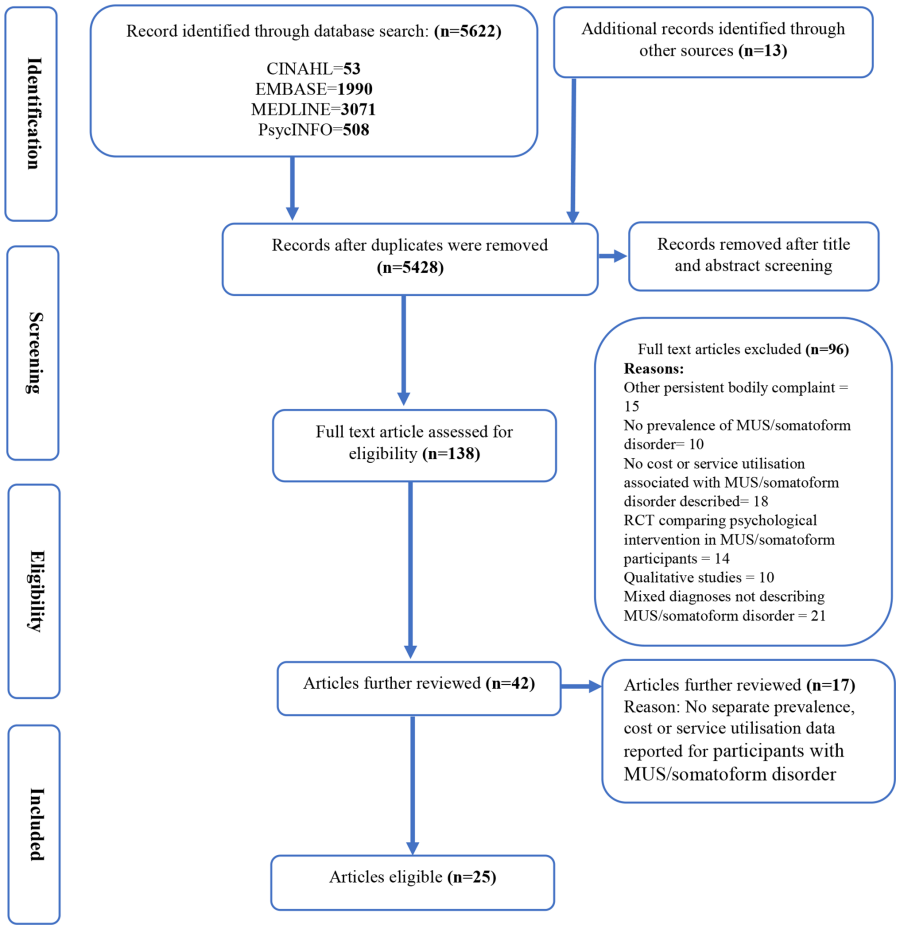

Figure 1 PRISMA flow diagram of the study selection process. MUS, medically unexplained symptoms; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, randomised controlled trial.

95% CI and median OR of costs or healthcare utilisation were extracted. In cases of insufficient data, authors were contacted at least twice by email.

RESULTS

Literature search

The search was updated at the time of manuscript preparation to capture recent and relevant studies. In total, the search strategy yielded 5622 articles. Additional reference searching and grey literature found 13 studies. After excluding 207 duplicates, the titles and abstracts of 5428 articles were screened for relevance. Title and abstract screening resulted in the exclusion of 5290 articles, mainly because these articles did not provide prevalence or healthcare utilisation cost/utilisation or were not primarily focused on MUS. Of the 138 full-text articles assessed, 113 were excluded at full-text review. Twenty-five articles were included in the final analysis. A flow diagram of the study identification process is presented in figure 1.

STUDY CHARACTERISTICS

Twenty-five studies[33–57] involving 31 650 individuals (high users) from 9 countries were included in the final analysis (figure 1). A great deal of variation was detected between studies regarding study design, including study setting, data source and collection, classification and measures used to define MUS and reported prevalence rates. Most studies were performed in the UK (n=8), followed by the USA (n=5), Germany (n=3) and Finland (n=3). Most studies were conducted in primary care or used primary care data (n=15), followed by secondary care (n=7) and a combination of primary and secondary care (n=3). Eight studies[33 35 36 38 41–43 51] had a cross-sectional design; nine were cohort studies,[46 48 49 52–57] seven[34 39 40 44 45 47 50] were case–control studies and one study[37] used case note review. Eighteen studies[33 35 36 39–45 47–50 52–54 56] employed a purposive sampling strategy to recruit patients and seven studies[34 37 38 46 51 55 57] recruited consecutive patients. Participants were predominantly female, constituting 66% of high users and 60.6% of comparators. Patients were slightly older in the comparator group (mean age: 71.3 years) compared with the high user group (mean age: 69.1 years). An overview of study characteristics can be found in table 2.

Study quality

None of the included studies had a low risk of bias in all criteria of the checklist adapted from the Ottawa-Newcastle Scale.[31] Sixteen[34 36 37 39–44 46 48–50 54 56 57] of the 25

Table 2 Study characteristics

				High users				Comparators			
Study	Year	Origin	Setting	Number of participants	Mean age (years) (SD)	Gender (% female)	Ethnicity (% white)	Number of participants	Mean age (years) (SD)	Gender (% female)	Ethnicity (% white)
Burton *et al*[33]	2011	UK	Primary and secondary care	267	Not reported	Not reported	Not reported	451	Not reported	Not reported	Not reported
Ferrari *et al*[34]	2008	Italy	Primary care	50	50.7 (12.9)	76	Not reported	50	38.8 (14.8)	56	Not reported
Gili *et al*[35]	2011	Spain	Primary care	318	53.3 (13.9)	67.6	Not reported	203	46.7 (14.3)	62.1	Not reported
Haas *et al*[36]	1999	USA	Primary and secondary care	69	65 (not reported)	64	93	Compared with normative data from another study			
Hansen *et al*[37]	2002	Denmark	Secondary care	294	Not reported	45.9	Not reported	Not reported	Not reported	Not reported	Not reported
Jacob *et al*[38]	2016	UK	Secondary care	100	Not reported	Not reported	Not reported	No control group			
Jyväsjärvi *et al*[39]	2001	Finland	Primary care	112	53.2 (not reported)	73.2	Not reported	106	51.3 (not reported)	70.8	Not reported
Jyväsjärvi *et al*[40]	1999	Finland	Primary care	113	52.4 (17.0)	72.6	Not reported	107	42.7 (20.6)	71.0	Not reported
Karlsson *et al*[41]	1999	Finland	Primary care	67	49.9 (not reported)	68.7	Not reported	No control group			
Katon *et al*[42]	1990	USA	Primary care	119	45.1 (12.6)	62.1	77.2	No control group			
Little *et al*[43]	2001	UK	Primary care	630	Not reported	68	98.1	1898	Not reported	57	98.7
McGorm *et al*[44]	2010	UK	Primary care	193	49 (10.0)	146(76)	Not reported	314	45.5 (11.5) 50.8 (10.3)	93 (61) 90 (59)	Not reported
Miranda *et al*[45]	1991	USA	Secondary care	54	50.1 (11.7)	34 (63)	14 (26)	160	52.1 (12.1)	92 (58)	70 (44)
Norton *et al*[46]	2012	France	Primary care	Data presented for overall population: 61.8% female, age: 42 (range: 18–93). Ethnicity not reported							
Patel *et al*[47]	2015	UK	Primary care	71	57 (19)	Not reported	Not reported	71	56 (18)	Not reported	Not reported
Portegijs *et al*[48]	1996	Netherlands	Primary care	45	37	56	Not reported	29	37	58	Not reported
Reid *et al*[49]	2002	UK	Secondary care	61	<46 39 (63.9) ≥46 22 (36.1)	41 (67.2)	51 (83.6) white 10 (16.4) non-white	219	<46. 99 (45.2) ≥46. 120 (54.8)	140 (63.9)	181 (82.6) white 38 (17.4) non-white
Schmitz and Kruse[50]	2002	Germany	Secondary care	389	45.4 (13.1)	63.7	Not reported	3337	40.8 (13.1)	48.2	Not reported
Schneider *et al*[51]	2011	Germany	Primary care	562	52.9 (17.5)	57.1	Not reported	159	33.5 (12.3)	83 (52.2)	Not reported
Smith *et al*[52]	1986	USA	Secondary care	41	44 (range: 21–73)	83.7	Not reported	No comparator			
Smith *et al*[53]	2002	USA	Primary care	104	41.3	83	Not reported	66	39.7	65	Not reported
Smits *et al*[54]	2009	Netherlands	Primary care	1008	15–65+	Not reported	Not reported	1601	15–65+	Not reported	Not reported
Taylor *et al*[55]	2012	UK	Primary care	410	41.6 (15.3)	71.2	White=75.1 Black=16.8 Asian=4.8 Other=3.3	No comparator			
van den Bussche[56]	2016	Germany	Primary and secondary care	23 590	73 (6.4)	46.3	Not reported	99 634	71.7 (6.1)	41.4	Not reported
Williams *et al*[57]	2001	UK	Secondary care	35	Not reported	Not reported	Not reported	182	Not reported	Not reported	Not reported

Table 3 Quality assessment of included studies

Reference	Selection of participants	Adequate description of study population	Validated method for ascertaining exposure	Validated method confirm outcome	Analysis and controls for confounders	Sample size calculation	Analytical methods appropriate
Burton *et al*[33]	Low risk	High risk	Unclear	Low risk	Unclear	Low risk	Low risk
Ferrari *et al*[34]	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Gili *et al*[35]	High risk	High risk	Low risk	Low risk	High risk	Unclear	Low risk
Haas *et al*[36]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Hansen *et al*[37]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Jacob *et al*[38]	Low risk	High risk	Low risk	High risk	Unclear	Unclear	Low risk
Jyväsjärvi *et al*[39]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Jyväsjärvi *et al*[40]	High risk	Low risk	High risk	Low risk	High risk	Unclear	Low risk
Karlsson *et al*[41]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Katon *et al*[42]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	Low risk
Little *et al*[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
McGorm *et al*[44]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
Miranda *et al*[45]	Low risk	High risk	Low risk	High risk	High risk	High risk	Low risk
Norton *et al*[46]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Patel *et al*[47]	Low risk	Unclear	Low risk	Low risk	High risk	High risk	Low risk
Portegijs *et al*[48]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Reid *et al*[49]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Schmitz and Kruse[50]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Schneider *et al*[51]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Smith *et al*[52]	Low risk	Unclear	Low risk	Low risk	High risk	Unclear	Low risk
Smith *et al*[53]	Low risk	Unclear	Low risk	Low risk	Unclear	High risk	Low risk
Smits *et al*[54]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Taylor *et al*[55]	Low risk	Unclear	Unclear	Low risk	High risk	High risk	Low risk
van den Bussche[56]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Williams *et al*[57]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	Low risk

'Low risk' indicates low risk of bias in that domain, 'high risk' indicates high risk of bias and 'unclear' indicates where risk of bias was unclear.

studies adequately described the study population (low risk of bias), and most studies[33 34 36–39 41–57] (n=23) clearly defined the selection of participants, with an adequate description of the target population and inclusion/exclusion criteria. Exposure and outcome were almost universally well described; 22 studies[34–39 41–54 56 57] presented valid measures for ascertaining exposure (the presence of MUS) and 23[33–37 39–44 46–57] used appropriate outcome measures (the prevalence of MUS in high users of healthcare and/or the magnitude of costs among high users of healthcare). The other two studies[38 45] did define the outcome measures but included these in subgroup analysis or cluster of symptoms. For all studies, the analytical approach used was considered appropriate. However, there were only two studies[33 43] where the risk of bias in sample size considered to be low, because of either the absence or poor quality of sample size calculation in all other studies. Table 3 displays the review quality scores per item based on the adapted Ottawa-Newcastle scale.[31]

Diagnostic tool/measures used

We noted diversity in the methods used to ascertain the presence of MUS. Online supplemental table 1 provides detailed descriptions of the diagnostic criteria and definitions of MUS used in the included studies. Four of the studies used a two-stage screening process.[34 35 37 41] Diagnostic instruments with structured interviews were used in 7 studies,[34 35 37 41 45 47 51] symptom checklists in 10 studies[36 39 40 42 46 48 50 52 54 56] and the somatic symptoms scale in 1 study.[43] In three studies, MUS was identified by data extraction from electronic patient records.[33 38 44] Furthermore, two studies used a GP assessment and rating sheet to ascertain MUS.[53 55]

There were a variety of different definitions and thresholds used to identify populations of high users of healthcare. Thresholds involving the number of contacts with healthcare providers were used in twelve studies.[35 38–41 43 44 47 48 51 53 56] However, there was considerable diversity in the cut-off chosen, and this ranged from three or more referrals in a 5 year period[44] to thirty or more consultations in 2 years.[47] Another definition used in four studies[37 49 50 54] involved a top percentage of healthcare users, ranging from the top 20% to the top 5%. One study defined high users as those who exceeded the mean number of visits within a year, or the top 50% of

healthcare users.[36] Ferrari and colleagues generated a list of individuals with the highest number of primary care contacts and worked down this list until fifty participants were recruited.[34] The definition of high users was unclear in two studies.[45 55]

Prevalence estimates

Online supplemental table 1 summarises prevalence rates and ORs of MUS in the included studies. Estimates of the prevalence of MUS ranged from 2.9%[57] to 76%[44] in high users of healthcare compared with between 1.1%[35] and 61%[44] in non-high user comparator groups. Only one of the 25 studies provided prevalence data by age group[49]; prevalence rates for those aged <46 years was 63.9% and 22% for those aged over 46 years in high users of healthcare compared with 45.2% for those aged <46 years and 54.8% for those aged ≥46 years in the non-high user group. Two studies provided prevalence rates of MUS by gender.[44 50] Prevalence rates ranged from 4.6% to 24% in males and from 8.3% to 76% in females in the high user group compared with from 2.9% to 39% in males and from 6.7% to 61% in females in the comparator group. Twelve studies[34 35 39 43 44 47–51 54 57] included a comparator group, of those 11 studies[34 35 39 43 44 47–51 54] reported a higher prevalence of MUS in high users of healthcare or 'high-cost' patients.

Seven studies[34 35 37 39 43 44 47] reported ORs instead of or in addition to prevalence estimates, to summarise the difference between MUS groups and comparators. The ratios reported in the included studies ranged from 1.45 to 17, and of these, none were less than 1 (ie, in favour of comparators vs MUS). All but one of the reported ORs indicated statistical significance, supporting the claim that MUS is more prevalent among high users of healthcare compared with those who are not. The only exception was that reported by Little and colleagues[43] when a cut-off score of 1–2 for the Somatic Symptom Inventory was used to define MUS (95% CI 0.81 to 1.62).

Two studies[48 56] used relative risk (RR) of being a high user of healthcare. Patients with MUS were twice as likely (RR: 2.33, 95% CI 2.20 to 2.50) to contact more than 10 different general practices and/or contact ≥3 different medical specialties.[56] Another study found that high healthcare utilisation was twice as high (RR: 2.0, 95% CI 1.10 to 3.60) in patients with a DSM-III-R diagnosis of somatisation.[48]

For the reader's interest, we calculated unadjusted ORs and 95% CIs for studies where these were not reported, using the number of events in the high user and non-high user groups where possible. These calculations were conducted for six studies,[35 49–51 54 57] and the results are summarised in online supplemental table 1, indicated by an asterisk. Generally, these ORs were greater than 1, suggesting that MUS is more prevalent among high healthcare users. There were two exceptions to this trend. The first was reported by Reid and colleagues, where participants aged ≥46 years who were in the top 5% of all outpatient appointments over a 3-year period had a lower prevalence of MUS compared with those who were not high healthcare users (22% vs 54.8%; unadjusted OR: 0.46, 95% CI 0.25 to 0.87).[49] The other exception was found by Williams and colleagues, where routine attenders to an emergency department were associated with higher rates of somatoform disorder compared with frequent attenders (3.8% vs 2.9%; unadjusted OR: 0.73, 95% CI 0.01 to 6.04).[57] These unadjusted ORs varied considerably, ranging from 0.46[49] to 6.75,[51] and CIs varied from narrow to as broad as 0.34–19.7,[35] suggesting that these anomalous results could be a product of the methodological heterogeneity between the studies.

Prevalence estimates according to diagnostic criteria

Numerous different criteria were used in the included studies to ascertain the diagnosis of MUS. The diagnostic criteria only used once included the DCPR,[34] the GHQ-28 somatisation subscale,[35] the Whitley index for somatisation,[37] the Somatic Symptom Inventory,[44] the International Classification of Primary Care code,[54] and diagnosis using the ICD-10 code for somatisation disorder.[56] Below, we summarise the prevalence estimates by grouping them according to diagnostic criteria used to define MUS.

Three studies[38 44 49] reported prevalence estimates of MUS derived from patients' medical records; the rates ranged from 22%[49] to 76%[44] in high users of healthcare compared with between 39% and 61%[44] in non-high user comparator groups. DSM-IV criteria for somatoform disorder were used to define MUS in four studies,[46 47 50 51] and the method used to collect the relevant information included PHQ-9,[46] PHQ-15[51] and diagnostic interviews.[47 50] The rates of MUS ranged from 4.6%[50] to 55.9%[51] among high users of healthcare, compared with 2.9%[50] to 15.8%[51] in non-high user comparator groups. Five studies[41 42 45 48 52] used interviews of differing formats to diagnose somatisation according to DSM-III criteria. The prevalence of somatisation among high healthcare users ranged from 20.2%[42] to 58%,[48] and of these 5 studies only Portegijs and colleagues reported prevalence of MUS among the comparator group (29%).[48] Two studies[36 39] reported prevalence rates of somatoform disorder defined by SCL-36 and SCL-90; the rates of somatoform disorder were 28.6% in the high user group compared with 16% in the non-high user group[39] and 56.5% in the high user group.[36] Further two studies reported prevalence rates using SCAN to diagnose MUS,[35 57] and prevalence among the high healthcare users ranged from 2.9%[57] to 17.3%,[35] and 3.4%[35] to 3.8%[57] among comparators. Finally, three studies used clinical assessments to diagnose MUS,[33 53 55] although only Smith and colleagues reported prevalence rates. These were only presented for the high healthcare user group as 61.2% in 1995, 17.8% in 1996 and 13.1% in 1997.[53]

Prevalence estimates according to different clinical settings

There were wide variations in the prevalence of MUS among high users in both primary care and secondary care settings. In primary care, prevalence estimates for

MUS ranged from 1.7%[35] to 76%[44] and in the secondary care setting from 4.6%[50] to 63.9%.[49] Given the large clinical heterogeneity between the studies included in this review, we determined not to proceed with a meta-analysis. The decision was also informed by the high risk of bias among the included studies due to insufficient attention to power.

Magnitude of healthcare costs

Only three studies included in the review investigated the magnitude of healthcare costs associated with the presence of MUS who are high users of healthcare.[33 49 52] The comparator group was different across these three studies, precluding pooling of healthcare cost estimates. Therefore, we have summarised the main findings descriptively. Burton and colleagues[33] compared individuals referred at least 3 times from primary to secondary care in the previous 5 years with MUS (repeatedly referred with MUS, RRMUS) with those infrequently referred (IRS) and those frequently referred with medically explained symptoms (RRMES). The RRMUS group was associated with significantly greater costs per patient over a 5-year period than the IRS group, with a difference of £3539 (95% CI 1458 to 5261) in inpatient costs, £778 (95% CI 705 to 852) in outpatient costs, £99 (95% CI 74 to 123) in emergency department costs, £260 (95% CI 224 to 296) in investigation costs and £4416 (95% 2315 to 6517) in total costs. The RRMUS group incurred greater investigation costs than the RRMES group, with an average difference of £102 per patient over 5 years (95% CI 56 to 149). However, there was no significant difference in the average inpatient, outpatient, emergency department or total costs between the RRMUS and RRMES groups (difference (95% CIs) = £491 (−1737 to 2718), £25 (−78 to 127), £22 (−7 to 52) and £537 (−1723 to 2798), respectively). Reid and colleagues[49] investigated frequent attenders of secondary care services and identified patients with MUS and compared their healthcare use and costs with patients without MUS. Patients with MUS were associated with greater mean costs of investigations (£244 vs £124, mean difference = £120, 95% CI 68 to 172) and mean total costs in secondary care (£955 vs £882, mean difference = £73, 95% CI 39 to 185). However, average costs per consultation episode in secondary care were lower for those with MUS than those without (£226 vs £230, mean difference = £104, 95% CI 72 to 136). Smith and colleagues[52] investigated healthcare utilisation of 41 patients meeting the essential features of somatisation disorder. Healthcare utilisation data were compiled in quarterly intervals. The mean inpatient charges averaged $599 (SD: ±$219), while outpatient charges averaged $215 (SD: ±$32). The mean combined charges (inpatient and outpatient) averaged $814 (SD: ±299).

DISCUSSION

The purpose of this review was to systematically investigate the existing literature to determine the prevalence of MUS in patients who are high users of healthcare and/or who accrue high healthcare costs and the magnitude of healthcare or associated costs. Although there is a vast body of literature estimating the prevalence of MUS and its associated costs, to the best of our knowledge, no previous study has focused on high users or high-cost patients. Our findings showed that there was great variation among studies on several different methodological parameters, including design; definitions and methods of identifying 'high use' or 'high-cost' populations; definitions and methods used to identify people with MUS within high use/high-cost populations; comparator groups; country and type of health service where the study was undertaken; and clinical setting (primary, secondary or ED).

Most studies adequately described the study population and inclusion/exclusion criteria. Exposure and outcome were almost universally well described and most studies used valid measures for ascertaining exposure (the presence of MUS) and outcome measures (the prevalence of MUS in high users of healthcare and/or the magnitude of costs among high users of healthcare). However, there was a 'high' risk of bias in most studies due to a lack of adequate consideration of power. Another frequently observed limitation was the lack of consecutive sampling in many studies, which could be explained by practical difficulties in reaching the target population. The degree of variation across the studies, combined with our quality findings that most studies were at high risk of bias, meant that we did not think it was appropriate to pool the results in a meta-analysis.

SUMMARY OF EVIDENCE

Prevalence estimates

The estimated prevalence of MUS was reported to be greater among high healthcare users compared with non-high user comparators for all but one of the 12 studies that included a comparator group[34 35 39 43 44 47–51 54 57]; however, these estimates varied considerably between studies. This is not surprising given the variability in methodology across the studies. Prevalence estimates by age and gender were poorly recorded. Only one study reported an overall higher prevalence of MUS among the non-high user comparator compared with the high user group.[57] This could partly be explained by a disparity in sample size between the groups, with fewer in the high user group (n=77) than the comparator group (n=182). The authors also suggest that this unexpected finding could be attributed to suboptimal sensitivity of the SCAN tool to identify somatoform autonomic disorder (F45.3). This study importantly highlights that not all patients with a somatoform disorder are high users of healthcare.

Only two studies reported MUS prevalence among high users according to gender,[43 49] and both found higher rates in females. One study provided prevalence estimates by age group,[48] and suggested high users were more likely to have MUS if they were aged under 46 years compared

with those who were older. A recent systematic review of the general characteristics of high-cost patients found costs were higher in older groups, but that mental health 'high-cost' patients tended to be younger.[58] Another study found that young adults (aged 18–24 years) with somatic symptoms and related disorders frequently used the healthcare system with substantial healthcare costs before and after diagnosis.[59] Despite the wide prevalence of MUS spectrum identified in this review, we believe MUS is a useful construct as it is consistently associated with increased morbidity and healthcare expenditure. Further research and interventions are required, incorporating a uniform definition and diagnostic approach.

Magnitude of cost

Only three studies[33 49 52] investigated the magnitude of healthcare costs associated with the presence of MUS who are high users of healthcare. Although they provided estimates of the magnitude of costs associated with MUS among adults who are high users of healthcare, the comparability of these studies was limited by heterogeneity in terms of study design, follow-up period, outcome measures and definitions of comparator group. Two of these studies[33 49] compared costs between those with MUS and those without, and unsurprisingly both reported greater investigation and total costs associated with MUS. The other study provided descriptions of quarterly inpatient and outpatient costs associated with somatisation disorder.[52] Our findings provide preliminary evidence to suggest that MUS is associated with greater healthcare costs, and interventions aimed at identifying and treating MUS early could help to reduce these costs in addition to improving patient outcomes. Healthcare costs per patients repeatedly referred with MUS over a 5-year period were considerably higher compared with those who were infrequently referred. Our results concur with those of a previous study showing costs of hospitalised patients with MUS to different wards across several hospitals between 2008 and 2018 in Northern Italy, in which the overall estimated costs of hospitalisation was €475 410 with a mean annual cost per patient of approximately €48 000.[60] In both general practices and outpatient clinics of a regional community mental health service in greater Rotterdam (the Netherlands), the mean direct (use of healthcare) and indirect costs (absenteeism and presenteeism) were estimated at €6815 per patient per year.[61] A recent systematic review investigating cost-of-illness studies and economic evaluations of MUS found that direct excess treatment costs (healthcare utilisation) per patient ranged from $432 to $5353 per year. There are also indirect costs (eg, presenteeism and sickness absence), which are estimated to be approximately seven times greater than the direct costs.[62]

Strengths and limitations

Several recent studies have found that mental health problems are common in high use or high-cost populations.[63–65] It is important, however, to begin to understand the nature of these mental health problems to plan effective interventions. This is the first systematic review to identify and present an in-depth synthesis of the best available evidence describing the prevalence of MUS in patients who are high users of healthcare and/or who accrue high healthcare costs. Strengths of this systematic review include the rigorous methodological approach employed using an established methodological framework.[17 30 31] Two independent reviewers were involved in study selection, data extraction and quality assessment, and a third reviewer was included to ensure overall methodological consistency and to resolve any disagreements. To ensure an exhaustive review of the available literature, a comprehensive search strategy was implemented with broad inclusion criteria. Additionally, the search was not restricted to the English language and grey literature sources were considered, to minimise the effects of language and publication bias, respectively. The search was repeated at the time of manuscript preparation to capture recent and relevant studies.

There are some limitations to the present study. First, the quality of these studies was variable and many did not report essential data, such as outcome measures, statistical power, reliability of measures and information about effect measures between intervention and control group. Second, given the limitations of the reported data, the high risk of bias among the included studies and the wide heterogeneity between them, we were unable to combine data in a meta-analysis, and instead results were reported as a narrative summary. Third, due to limited data on gender and age, we were unable to adequately measure the effect of these variables, although this represents an important area for future research. We also planned to assess publication bias but were unable to do so owing to the wide heterogeneity between the included studies. The generalisability of these findings may be uncertain, although each setting is inevitably unique and healthcare professionals may use different assessment criteria to ascertain MUS and definitions to identify high or costly healthcare users.

Implications of results

The findings suggest that people with MUS are overrepresented in populations of high users of healthcare and high-cost patients, accounting for a disproportionate amount of healthcare use in both primary and secondary care settings. Given the use of healthcare resources by this population and the associated costs, interventions to identify those with MUS and to deliver targeted psychological interventions may reduce healthcare costs, optimise pharmacological interventions and improve integration of primary and secondary care while improving overall patient outcomes. van den Bussche and colleagues[56] argue that frequent attendance appears to involve various aspects of the healthcare system, including healthcare providers, patients and the disparaging healthcare system, contributing to high utilisation. Strategies to reduce

healthcare costs should, therefore, carefully consider these systemic issues.

In terms of future research, our findings demonstrate a clear need for a standardised approach to understanding MUS and high users of healthcare. There was a great deal of variety of methods used to ascertain the presence of MUS and to identify those who are high healthcare users. An agreed definition of MUS is required to allow comparison and synthesis of findings in the academic literature.[66] Similarly, a universal definition of high healthcare users would be helpful to integrate the estimates of sociodemographic and clinical characteristics of this high-need group. Hayes and colleagues found that there was significant variation in healthcare use and costs among those with high needs, defined as those with three or more chronic diseases associated with a functional impairment.[67]

CONCLUSION

MUS is common among adults who are high users of healthcare and/or who accrue high healthcare costs. The present review quantifies the prevalence of MUS among high healthcare users and describes estimates of costs associated with this population. Significant heterogeneity was found between the included studies, particularly pertaining to methods of ascertaining MUS and definitions of high healthcare users, in addition to high risk of bias among the studies. These factors precluded meta-analysis. Nonetheless, this review indicates that this group of patients incurs a disproportionate level of healthcare resources compared with the general population, which should be considered by policymakers, clinicians and researchers. It also indicates that this group of individuals pursues specific form of health-seeking behaviour that should be adequately understood and addressed. Future studies should consider approaches to high users associated with MUS by carefully and consistently defining frequent attendance, measures used to define MUS and the study setting.

Dissemination

Any data generated from this systematic review will be made available from the corresponding author on reasonable request.

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Contributors All authors contributed to the focus of this systematic review topic and approved the final version for publication. FJ drafted the initial manuscript with guidance and feedback from DR, EG and AB at all stages. FJ drafted the final version, performed the search and is a guarantor. The search strategy was developed by FJ and iteration discussed with OL, EG and AB. FJ and OL performed the initial screening and study selection. FJ and DR collected data from the included studies, conducted quality assessment, performed data analysis/synthesis, drafted and critically reviewed the manuscript. EG ensured data extraction consistency.

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PRISMA 2020 Checklist

PREVALENCE OF MEDICALLY UNEXPLAINED SYMPTOMS IN ADULTS WHO ARE HIGH USERS OF HEALTHCARE SERVICES AND MAGNITUDE OF ASSOCIATED COSTS: A SYSTEMATIC REVIEW

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7 & 29
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10-11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 13-14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 10-11

PRISMA 2020 Checklist

PREVALENCE OF MEDICALLY UNEXPLAINED SYMPTOMS IN ADULTS WHO ARE HIGH USERS OF HEALTHCARE SERVICES AND MAGNITUDE OF ASSOCIATED COSTS: A SYSTEMATIC REVIEW

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9-10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9-10
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 11
Study characteristics	17	Cite each included study and present its characteristics.	Page 12-13
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 17-21
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 17-21
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 23-27
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 16
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 22
	23b	Discuss any limitations of the evidence included in the review.	Page 25
	23c	Discuss any limitations of the review processes used.	Page 25

PRISMA 2020 Checklist

PREVALENCE OF MEDICALLY UNEXPLAINED SYMPTOMS IN ADULTS WHO ARE HIGH USERS OF HEALTHCARE SERVICES AND MAGNITUDE OF ASSOCIATED COSTS: A SYSTEMATIC REVIEW

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 27
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO: CRD42018100388
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Review protocol published in BMJOpen: https://bmjopen.bmj.com/content/9/7/e027922
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This research received no specific grant from any funding agency
Competing interests	26	Declare any competing interests of review authors.	None declared
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Provided as supplementary materials as part of this submission

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Medline search term – OVID interface

Part 1: Setting

1	*health care/
2	(health adj5 care).ti,ab,de.
3	*health service/
4	(health adj5 service$).ti,ab,de.
5	*hospital/
6	hospital$.ti,ab,de.
7	*ambulatory care/
8	(ambulatory care adj5 facilit$).ti,ab,de.
9	*outpatient/
10	outpatient$.ti,ab,de.
11	*outpatient department/
12	(outpatient adj2 department).ti,ab,de.
13	*outpatient department/
14	(outpatient adj2 clinic$).ti,ab,de.
15	primary medical care/
16	(primary adj2 care).ti,ab,de.
17	*general practice/
18	(general adj practi$).ti,ab,de.
19	family practice.mp.
20	(family adj practi$).ti,ab,de.
21	gp.mp.
22	gps.ti,ab,de

23	family physician.mp.
24	family physic$.ti,ab,de.
25	*emergency health service/
26	emergency service$.ti,ab,de.
27	(emergency adj2 service$).ti,ab,de.
28	emergency department.mp. or *emergency ward/
29	emergency department$.ti,ab,de.
30	(emergency adj5 department$).ti,ab,de.
31	*medical service/
32	(medical adj5 service).ti,ab,de.
33	exp delivery of health care/
34	exp health service$/
35	exp ambulatory care facilities/
36	exp ambulatory care information systems/
37	exp primary care/
38	exp physicians, family/
39	exp primary health care/

Part 2: Cost/service utilisation

1	high cost.mp.
2	high cost$.ti,ab,de.
3	high?cost$.ti,ab,de.
4	(high adj5 cost$).ti,ab,de.
5	frequent cost.mp.
6	frequent cost$.ti,ab,de.

7	(frequent adj5 cost$).ti,ab,de.
8	high expenditure.mp.
9	high expenditure.ti,ab,de.
10	(high adj5 expenditure).ti,ab,de.
11	high expense.mp.
12	high expense.ti,ab,de.
13	(high adj5 expense).ti,ab,de.
14	frequent user.mp.
15	frequent user.ti,ab,de.
16	(frequent adj5 user).ti,ab,de.
17	high user.mp.
18	high user.ti,ab,de.
19	(high adj5 user).ti,ab,de.
20	high utiliser.mp.
21	high utiliser$.ti,ab,de.
22	high utilizer.mp.
23	high utilizer$.ti,ab,de.
24	(high adj5 utiliser$).ti,ab,de.
25	(high adj5 utilizer$).ti,ab,de.
26	frequent utiliser.mp.
27	frequent utilizer.mp.
28	frequent utilizer$.ti,ab,de.
29	frequent utiliser$.ti,ab,de.
30	(frequent adj5 utilizer$).ti,ab,de.

31	(frequent adj5 utiliser$).ti,ab,de.
32	high utilisation.mp.
33	high utilization.mp.
34	high utilization.ti,ab,de.
35	high utilisation.ti,ab,de.
36	(high adj5 utilization).ti,ab,de.
37	(high adj5 utilisation).ti,ab,de.
38	frequent utilisation.mp.
39	frequent utilization.mp.
40	frequent utilisation.ti,ab,de.
41	frequent utilization.ti,ab,de.
42	(frequent adj5 utilisation).ti,ab,de.
43	(frequent adj5 utilization).ti,ab,de.
44	high need.mp.
45	high need.ti,ab,de.
46	(high adj5 need).ti,ab,de.
47	high attend.mp.
48	high attend$.ti,ab,de.
49	(high adj5 attend$).ti,ab,de.
50	superutilizer.mp.
51	superutilizer.ti,ab,de.
52	exp health expenditures/
53	exp patient acceptance of health care/
54	exp health care costs/

55	exp health services accessibility/
56	exp cost benefit analysis/
57	exp practice patterns physicians/
58	exp efficiency organizational/
59	exp health services misuse/
60	exp patient care team/
61	exp case management/
62	exp office visits/
63	exp referral/

Part 3: MUS Umbrella term

1	exp fatigue syndrome chronic/
2	*chronic fatigue syndrome/
3	chronic fatigue.ti,ab,de.
4	fatigue syndrome.ti,ab,de.
5	myalgic encephalomyelitis.mp.
6	myalgic encephalomyelitis.ti,ab,de.
7	exp irritable bowel syndrome/
8	irritable bowel syndrome.mp.
9	irritable bowel.ti,ab,de.
10	functional colonic disease.mp.
11	functional colonic disease.ti,ab,de.
12	functional gastrointestinal disorder.mp.
13	functional gastrointestinal disorder.ti,ab,de.

14	exp fibromyalgia/
15	exp chronic pain/
16	*fibromyalgia/
17	fibromyalgia$.ti,ab,de.
18	*chronic pain/
19	chronic pain.ti,ab,de.
20	pain disorder.mp.
21	pain disorder.ti,ab,de.
22	exp somatoform disorders/
23	somatoform.mp.
24	somatoform.ti,ab,de.
25	exp hysteria/
26	hysteri.mp.
27	hysteri$.ti,ab,de.
28	somatiz.mp.
29	somatiz$.ti,ab,de.
30	somatis.mp.
31	somatis$.ti,ab,de.
32	medically unexplained.ti,ab,de.
33	medically unexplained.mp.
34	functional somatic.mp.
35	functional somatic.ti,ab,de.
36	psychosom.mp.
37	psychosom$.ti,ab,de.

38	nonorganic.mp.
39	nonorganic.ti,ab,de.
40	non-organic.mp.
41	non-organic.ti,ab,de.
42	psychogen.mp.
43	psychogen.ti,ab,de.
44	*conversion disorder/
45	conversion dosorder.ti,ab,de.
46	conversion symptoms.mp.
47	conversion symptoms.ti,ab,de.
48	functional motor symptoms.mp.
49	functional motor symptoms.ti,ab,de.
50	functional movement disorder.mp.
51	fucntional movement disorder.ti,ab,de.
52	exp Hypochondriasis/
53	*hypochondriasis/
54	hypochondriasis.ti,ab,de.
55	fucntional syndrome.mp.
56	(functional adj syndrome$).ti,ab,de.
57	*psychosomatic disorder/
58	psychosomatic disorder.ti,ab,de.
59	exp psychophysiologic disorder$/
60	psychophysiologic disorder.mp.
61	(psychophysiologic adj disorder).ti,ab,de.

62	exp somatoform disorder$/
63	*somatoform disorder/
64	(somatoform adj disorder).ti,ab,de.
65	exp factitious disorder$/
66	(factitious adj disorder$).ti,ab,de.
67	factitious disorder.mp.
68	health anxiety.mp.
69	(health adj anxiety).ti,ab,de.

EMBASE search terms – OVID interface

Part 1: Setting

1	*health care/
2	(health adj5 care).ti,ab,de.
3	*health service/
4	(health adj5 service$).ti,ab,de.
5	*hospital/
6	hospital$.ti,ab,de.
7	*ambulatory care/
8	(ambulatory care adj5 facilit$).ti,ab,de.
9	*outpatient/
10	outpatient$.ti,ab,de.
11	*outpatient department/
12	(outpatient adj2 department).ti,ab,de.
13	*outpatient department/

14	(outpatient adj2 clinic$).ti,ab,de.
15	primary medical care/
16	(primary adj2 care).ti,ab,de.
17	*general practice/
18	(general adj practi$).ti,ab,de.
19	family practice.mp.
20	(family adj practi$).ti,ab,de.
21	gp.mp.
22	gps.ti,ab,de
23	family physician.mp.
24	family physic$.ti,ab,de.
25	*emergency health service/
26	emergency service$.ti,ab,de.
27	(emergency adj2 service$).ti,ab,de.
28	emergency department.mp. or *emergency ward/
29	emergency department$.ti,ab,de.
30	(emergency adj5 department$).ti,ab,de.
31	*medical service/
32	(medical adj5 service).ti,ab,de.
33	exp delivery of health care/
34	exp health service$/
35	exp ambulatory care facilities/
36	exp ambulatory care information systems/
37	exp primary care/

38	exp physicians, family/
39	exp primary health care/

Part 2: Cost/service utilisation

1	high cost.mp.
2	high cost$.ti,ab,de.
3	high?cost$.ti,ab,de.
4	(high adj5 cost$).ti,ab,de.
5	frequent cost.mp.
6	frequent cost$.ti,ab,de.
7	(frequent adj5 cost$).ti,ab,de.
8	high expenditure.mp.
9	high expenditure.ti,ab,de.
10	(high adj5 expenditure).ti,ab,de.
11	high expense.mp.
12	high expense.ti,ab,de.
13	(high adj5 expense).ti,ab,de.
14	frequent user.mp.
15	frequent user.ti,ab,de.
16	(frequent adj5 user).ti,ab,de.
17	high user.mp.
18	high user.ti,ab,de.
19	(high adj5 user).ti,ab,de.
20	high utiliser.mp.
21	high utiliser$.ti,ab,de.

22	high utilizer.mp.
23	high utilizer$.ti,ab,de.
24	(high adj5 utiliser$).ti,ab,de.
25	(high adj5 utilizer$).ti,ab,de.
26	frequent utiliser.mp.
27	frequent utilizer.mp.
28	frequent utilizer$.ti,ab,de.
29	frequent utiliser$.ti,ab,de.
30	(frequent adj5 utilizer$).ti,ab,de.
31	(frequent adj5 utiliser$).ti,ab,de.
32	high utilisation.mp.
33	high utilization.mp.
34	high utilization.ti,ab,de.
35	high utilisation.ti,ab,de.
36	(high adj5 utilization).ti,ab,de.
37	(high adj5 utilisation).ti,ab,de.
38	frequent utilisation.mp.
39	frequent utilization.mp.
40	frequent utilisation.ti,ab,de.
41	frequent utilization.ti,ab,de.
42	(frequent adj5 utilisation).ti,ab,de.
43	(frequent adj5 utilization).ti,ab,de.
44	high need.mp.
45	high need.ti,ab,de.

46	(high adj5 need).ti,ab,de.
47	high attend.mp.
48	high attend$.ti,ab,de.
49	(high adj5 attend$).ti,ab,de.
50	superutilizer.mp.
51	superutilizer.ti,ab,de.
52	exp health expenditures/
53	exp patient acceptance of health care/
54	exp health care costs/
55	exp health services accessibility/
56	exp cost benefit analysis/
57	exp practice patterns physicians/
58	exp efficiency organizational/
59	exp health services misuse/
60	exp patient care team/
61	exp case management/
62	exp office visits/
63	exp referral/

Part 3: MUS Umbrella term

1	exp fatigue syndrome chronic/
2	*chronic fatigue syndrome/
3	chronic fatigue.ti,ab,de.
4	fatigue syndrome.ti,ab,de.
5	myalgic encephalomyelitis.mp.

6	myalgic encephalomyelitis.ti,ab,de.
7	exp irritable bowel syndrome/
8	irritable bowel syndrome.mp.
9	irritable bowel.ti,ab,de.
10	functional colonic disease.mp.
11	functional colonic disease.ti,ab,de.
12	functional gastrointestinal disorder.mp.
13	functional gastrointestinal disorder.ti,ab,de.
14	exp fibromyalgia/
15	exp chronic pain/
16	*fibromyalgia/
17	fibromyalgia$.ti,ab,de.
18	*chronic pain/
19	chronic pain.ti,ab,de.
20	pain disorder.mp.
21	pain disorder.ti,ab,de.
22	exp somatoform disorders/
23	somatoform.mp.
24	somatoform.ti,ab,de.
25	exp hysteria/
26	hysteri.mp.
27	hysteri$.ti,ab,de.
28	somatiz.mp.
29	somatiz$.ti,ab,de.

30	somatis.mp.
31	somatis$.ti,ab,de.
32	medically unexplained.ti,ab,de.
33	medically unexplained.mp.
34	functional somatic.mp.
35	functional somatic.ti,ab,de.
36	psychosom.mp.
37	psychosom$.ti,ab,de.
38	nonorganic.mp.
39	nonorganic.ti,ab,de.
40	non-organic.mp.
41	non-organic.ti,ab,de.
42	psychogen.mp.
43	psychogen.ti,ab,de.
44	*conversion disorder/
45	conversion dosorder.ti,ab,de.
46	conversion symptoms.mp.
47	conversion symptoms.ti,ab,de.
48	functional motor symptoms.mp.
48	fnctional motor symptoms.ti,ab,de.
49	functional movement disorder.mp.
50	fucntional movement disorder.ti,ab,de.
51	exp Hypochondriasis/
52	*hypochondriasis/

53	hypochondriasis.ti,ab,de.
54	fucntional syndrome.mp.
55	(functional adj syndrome$).ti,ab,de.
56	*psychosomatic disorder/
57	psychosomatic disorder.ti,ab,de.
58	exp psychophysiologic disorder$/
59	psychophysiologic disorder.mp.
60	(psychophysiologic adj disorder).ti,ab,de.
61	exp somatoform disorder$/
62	*somatoform disorder/
63	(somatoform adj disorder).ti,ab,de.
64	exp factitious disorder$/
65	(factitious adj disorder$).ti,ab,de.
66	factitious disorder.mp.
67	health anxiety.mp.
68	(health adj anxiety).ti,ab,de.

CINAHL – EBSCO interface

Part 1: Setting

1	health N5 care
2	health N5 service*
3	Hospital*.mp
4	ambulatory care
5	ambulatory N5 facilities

6	outpatient*
7	outpatient N2 department
8	outpatient N2 clinic*.
9	primary care
10	primary N2 care.
11	general
12	family N practi*
13	gp
14	gps
15	Family physic*.
16	Emergency service*
17	emergency N2 service*
18	emergency department*
19	emergency N5 department*
20	Medical N5 service
21	Delivery of health care+
22	Health service*+
23	Ambulatory care facilities+
24	Ambulatory care Information systems+
25	Primary care+
26	Physicians, family+
27	primary health care+

Part 2: Cost/service utilisation

1	high cost*
2	high?cost*
3	high N5 cost*
4	frequent cost*
5	frequent N5 cost*
6	high N5 expenditure
7	high expense
8	high N5 expense
9	frequent user
10	frequent N5 user
11	high user
12	high Nj5 user
13	high utiliser*
14	high N5 utiliser*
15	high utilizer*
16	high N5 utilizer*
17	frequent utilizer*
18	frequent N5 utilizer*
19	frequent utiliser*
20	frequent adj5 utiliser*
21	high utilization
22	high N5 utilization
23	high utilisation
24	high N5 utilisation

25	frequent utilisation
26	frequent N5 utilisation
27	frequent utilization
28	frequent N5 utilization
29	high need
30	high N5 need
31	high attend*
32	high N5 attend*
33	frequent attend*
34	frequent N5 attend*
35	Superutilizers+
36	superutilizer
37	Health expenditures+
38	Patient Acceptance of Health Care+
39	Health care costs+
40	Health services accessibility+
41	cost-benefit analysis+
42	practice patterns, physicians+
43	efficiency, organizational+
44	health services misuse+
45	Patient care team+
46	case management+
47	office visits+
48	referral+

Part 3: MUS umbrella term

1	Fatigue syndrome, chronic+
2	chronic fatigue+
3	fatigue syndrome+
4	myalgic encephalomyelitis+
5	irritable bowel syndrome+
6	irritable bowel
7	functional colonic disease
8	functional gastrointestinal disorder
9	Fibromyalgia+
10	chronic pain+
11	fibromyalgia*
12	chronic pain
13	pain disorder
14	somatoform disorders+
15	Somatoform
16	hysteria+
17	Hysteri*
18	Somatiz*
19	Somatis*
20	medically unexplained
21	functional somatic
22	Psychosom*
23	Nonorganic
24	non-organic

25	Psychogen
26	conversion disorder
27	conversion symptoms
28	functional motor symptoms
29	functional movement disorder
30	Hypochondriasis+
31	Hypochondriasis
32	(functional N syndrome*)
33	(psychosomatic N disorder*)
34	psychophysiologic disorder*+
35	(psychophysiologic N disorder)
36	somatoform disorder*+
37	(somatoform N disorder)
38	factitious disorder*+
39	(factitious N disorder*)
40	(health N anxiety)

PsycINFO – OVID interface

Part 1: Setting

1	health care.tw
2	health adj5 care
3	health service.tw
4	health adj5 service$
5	hospital.tw
6	hospital$.mp

7	ambulatory care.tw
8	ambulatory care adj5 facilit$.mp
9	outpatient.tw
10	outpatient$.mp
11	outpatient department.tw
12	outpatient adj2 department.mp
13	outpatient clinic.tw
14	outpatient adj2 clinic$.mp
15	primary care.tw
16	primary adj2 care.mp
17	general.tw
18	family.tw
19	general or family adj practi$.mp
20	gp.tw
21	gp or gps.mp
22	family physician.tw
23	Family physic$.mp
24	Emergency service.tw
25	Emergency service$.mp
26	Emergency adj2 service$.mp.
27	Emergency department.tw
28	Emergency department$.mp
29	Emergency adj5 department$.mp.
30	Medical service.tw

31	Medical adj5 service.mp.
32	Delivery of health care.mp
33	Delivery of health care.tw
34	Health service$.mp
35	Health service.tw
36	Ambulatory care facilities.mp
37	Ambulatory care facilities.tw
38	Ambulatory care Information systems.mp
39	Ambulatory care information systems.tw
40	Primary care.mp
41	Primary care.tw
42	Physicians, family.mp
43	Physicians, family.tw
44	primary health care.mp
45	primary health care.tw

Part 2: Cost/service utilisation

1	high cost.tw
2	high cost$.mp
3	high? cost$.mp
4	high adj5 cost$.mp
5	Frequent cost.tw
6	frequent cost$.mp
7	frequent adj5 cost$.mp

8	high expenditure.tw
9	high expenditure.mp
10	high adj5 expenditure.mp
11	High expense.tw
12	high expense.mp
13	high adj5 expense.mp
14	Frequent user.tw
15	frequent user.mp
16	frequent adj5 user.mp
17	high user.tw
18	high user.mp
19	high adj5 user.mp
20	high utilise.tw
21	high utiliser$.mp
22	high adj5 utiliser$.mp
23	high utilize.tw
24	high utilizer$.mp
25	high adj5 utilizer$.mp
26	frequent utilize.tw
27	frequent utilizer$.mp
28	frequent adj5 utilizer$,mp
29	frequent utilise.tw
30	frequent utiliser$.mp
31	frequent adj5 utiliser$.mp

32	high utilization.tw
33	high utilization.mp
34	high adj5 utilization.mp
35	high utilisation.tw
36	high utilisation.mp
37	high adj5 utilisation.mp
38	Frequent utilisation.tw
39	frequent utilisation.mp
40	frequent adj5 utilisation.mp
41	frequent utilization.mp
42	frequent adj5 utilization.mp
43	High need.tw
44	high need.mp
45	high adj5 need.mp
46	high attend.tw
47	high attend$.mp
48	high adj5 attend$.mp
49	Frequent attend.tw
50	frequent attend$.mp
51	frequent adj5 attend$.mp
52	superutilizers.tw
53	Superutilizers.mp
54	Health expenditures.mp
55	Health expenditure.tw

56	Patient Acceptance of Health Care.mp
57	Patient acceptance of health care.tw
58	Health care costs.mp
59	Health care costs.tw
60	Health services accessibility.mp
61	Health services accessibility.tw
62	cost-benefit analysis.mp
63	cost-benefit analysis.tw
64	practice patterns, physicians.mp
65	practice patterns, physicians.tw
66	efficiency, organizational.mp
67	efficiency, organizational.tw
68	health services misuse.mp
69	health services misuse.tw
70	Patient care team.mp
71	Patient care team.tw
72	case management.mp
73	case management.tw
74	office visits.mp
75	office visits.tw
76	referral.mp
77	referral.tw

Part 3: MUS umbrella term

1	chronic fatigue.tw
2	Fatigue syndrome, chronic.mp
3	Fatigue syndrome, chornic.tw
4	chronic fatigue.mp
5	fatigue syndrome.tw
6	fatigue syndrome.mp
7	myalgic encephalomyelitis.tw
8	myalgic encephalomyelitis.mp
9	irritable bowel syndrome.tw
10	irritable bowel syndrome.mp
11	functional colonic disease.tw
12	functional colonic disease.mp
13	functional gastrointestinal disorder.tw
14	functional gastrointestinal disorder.mp
15	fibromyalgia.tw
16	fibromyalgia,mp
17	fibromyalgia$.mp
18	chronic pain.tw
19	chronic pain.mp
20	chronic disorder.tw
21	pain disorder.mp
22	somatoform disorders.mp
23	somatoform disorders.tw

24	somatoform.mp
25	somatoform.tw
26	hysteria.tw
27	hysteri$.mp
28	somatis.tw
29	somatiz.tw
30	somatiz$.mp
31	somatis$.mp
32	medically unexplained.tw
33	medically unexplained.mp
34	functional somatic.tw
35	functional somatic.mp
36	psychosom.tw
37	psychosom$.mp
38	nonorganic.tw
39	non-organic.tw
40	nonorganic.mp
41	non-organic.mp
42	psychogen.tw
43	psychogen.mp
44	Conversion disorder.tw
45	conversion disorder.mp
46	conversion symptoms.mp
47	functional motor symptoms.tw

48	functional movement disorder.tw
49	functional motor symptoms.mp
50	functional movement disorder.mp
51	hypochondriasis.mp
52	Hypochondriasis.tw
53	Functional syndrome.tw
54	functional adj syndrome$.mp
55	psychosomatic disorder.tw
56	psychosomatic adj disorder$.mp
57	psychophysiologic disorder$.mp
58	psychophysiologic adj disorder.mp
59	psychophysiologic disorder.tw
60	somatoform disorder$.mp
61	somatoform disorder.tw
62	Somatoform disorder.mp
63	somatoform adj disorder.tw
64	factitious disorder$.mp
65	factitious disorder.mp
66	factitious disorder.tw
67	factitious adj disorder$.mp
68	Health anxiety.tw
69	Health anxiety.mp
70	health adj anxiety.mp

Quality assessment form adapted from the Ottawa-Newcastle scale (NOS) for assessing non-randomised studies

		Yes/No/Unclear
Selection of participants	[1] Was the inclusion/exclusion clearly described? (for example, age, diagnosis status, MUS) [2] Was inclusion/exclusion assessed using valid and reliable measures? (for example, clinical interview to ascertain MUS or standardised questionnaires) [3] Was recruitment strategy clearly described? [4] Did the investigators ensure that the exposed/unexposed group were comparable (for example did they use stratification or matching)	
Adequate description of study population	[1] Was study population well characterised? ➢ Age ➢ Sex ➢ Ethnicity ➢ Suitable definition of MUS	
Validated method for ascertaining exposure	[1] Was the method used to ascertain exposure clearly defined? [2] Was a valid and reliable measure used to ascertain exposure? (For example what measures were used to confirm MUS) ➢ Standardised questionnaires ➢ Clinical interview	
Validated method to confirm outcome	[1] Was a valid and reliable measures used to ascertain outcome? For example ➢ Mean change in health expenditure ➢ Interviews ➢ Questionnaires	
Adequate follow-up period	[1] Was the follow-up long enough for the outcome to occur? [2] Was the follow-up period the same across all groups?	
Adequate follow-up period	[1] Was follow-up adequate enough for the outcome to occur? [2] Was follow-up period the same across groups? [3] Were differences in follow-up adjusted for using statistical techniques?	
Completeness of follow-up (attrition)	[1] Were drop-out rates and reasons for drop-out similar across exposed and unexposed? [2] Were numbers of dropouts/withdrawals documented at each time point?	
Analysis and controls for confounders	[1] Does the study identify and control for confounders or effect modifiers?	
Sample size calculation	[1] Is the sample size adequate [2] Did the study describe how the sample size was calculated? [3] Was the sample size large enough to detect differences in events between groups? Mean change	
Analytical methods appropriate	[1] What kind of analysis done appropriate for the kind of outcome data? For example, ➢ Continuous – Mixed model, ANCOVA ➢ Categorical - Mixed model for categorical outcome ➢ Dichotomous – Logistic regression [2] Was lost to follow-up accounted for in the analysis (e.g. through sensitivity analysis)	

Data extraction form adapted from Hayden and colleagues Framework

Abbreviation

MUS	Medically Unexplained Symptoms
SSD	Somatic Symptoms Disorder
IBS	Irritable Bowel Syndrome
GP	General Practitioner
BDS	Bodily Distress Syndrome
EX	Excluded
NR	Not Reported

Eligibility criteria for the title and abstract screening phase

Study design	**Assessment**	**Comment**
Is it: [1] A cohort study (prospective or retrospective) [2] A case-control or nested case-control [3] A cross-sectional study	 Yes No Unclear	
Population		
[1] Were patients high users of healthcare [2] Accrue high healthcare costs Including: high cost patients, high users, distressed high users, utilisers of care, frequent attenders in primary care, frequent attenders at an emergency department. Please answer yes if high users or high cost patients included as a sub-group. [3] Were patients with MUS included in the study defined by a recognised measure including: a standardised research interview (e.g. the Structured Clinical Interview for Mental Disorders) to generate a diagnosis of a somatoform disorder according to: DSM-III; DSM-IV-R; DSM V; ICD-9; ICD-10; or other relevant diagnostic system; a clinical assessment leading to a clinical diagnosis of a somatoform disorder according to any of the above diagnostic systems; a validated scale for the assessment of MUS, such as the Screening for Somatoform Disorders, the Bradford Somatic Inventory, or component subscales of validated standardised instruments for the assessment of general psychopathology or general health status, such as the Patient Health Questionnaire-15 (PHQ-15); or an assessment which generated a recognised symptom grouping of MUS developed for research purposes (e.g. abridged somatisation disorder, multi-somatoform disorder, bodily distress disorder, and complex somatic symptom disorder . **NB:** Please answer YES if MUS is diagnosed as a sub group	Yes No Unclear	
Are patients aged (18 years or above) **NB:** Please answer Yes if mixed age population	Yes No Unclear	
Outcomes		

Did the study report any of the following outcomes: [1] Prevalence of MUS [2] Patient characteristics and context associated with high service usage/costs among patients with MUS [3] Magnitude or risk of cost or use of healthcare associated with the presence of MUS		
Follow-up		
Were the patients followed up and adequate measures taken **NB:** Please answer Yes if adequate measure were taken and key characteristics described	Yes No Unclear	
Final decision (please tick)	Include Exclude Unclear	

Exclusion criteria

Reasons for exclusion of study from review (please circle where appropriate)	
Methods	[1] Not a cohort/case-control or cross-sectional study [2] Qualitative study
Patients	Age: <18 Physical illness/psychiatric condition: [1] Paediatric patients [2] Palliative care [3] Obstetrics [4] Patients in acute mental health settings
Intervention	[1] Testing of any intervention [2] Screening
Outcomes	No relevant outcomes assessed No data for relevant subgroup extractable
Follows-up period	No follow-up
Other	Duplicate publication Other

Inclusion criteria

Specific inclusion criteria (please include if answer is Yes to all question below)	
Eligibility criteria	
Satisfaction of eligibility criteria	Yes No Unclear
Effect sizes	
Is there sufficient reporting of statistics or data to calculate effect sizes	Yes No Unclear

Organisation

Organisational aspect		**Exclude**		**Include**
Reviewer/date:		**Checked by:**		
Author/Year				
Journal/Source				
Country of origin				

Publication type	Full text/Abstract/Book chapter/progress report/ Other – please specify			
Fate	Decision: pending/Checked reference/Use for discussion/EX without listing/EX with listing Other – please specify			
Notes				

Study characteristics

General study characteristics (please circle where appropriate)	
Location of study	
Study aims	Reported/NR
Date of recruitment	From_____ to_____ Median (range):# Mean:#
Length of follow-up of outcome of interest + length of follow-up of study	From_____ to_____ Median (range):# Mean:#
Outcome assessed	Did the study report any of the following outcome: [1] Prevalence of MUS [2] Patients characteristics and context associated with high service usage/costs among patients with MUS [3] Magnitude of cost or use of healthcare associated with the presence of MUS Other *(please specify)*
Outcome definition	
Relationship between outcome and relevant factor	Is the relationship statistically significant? Yes/No OR/mean difference:# If No, is it due to: Low powered or inconclusive study/A true negative study
Power calculation	Yes/No/Not reported Calculated sample size:# Sample size achieved: Yes/No
Funding	Unclear NR Please state where reported
Conflict of interest statement	Yes/No/NR

Baseline characteristics of patients (**please circle where appropriate**)			
	Exposure	Control	Notes: Any relationship with outcomes? Yes/No/NR If Yes Please state if statistically significant and OR/mean changes in continuous values
Overall comment: Significant/Insignificant			
Number of patients			
Age range (if reported0 Mean			
Ethnicity No%			
Gender No%	Male: Female:	Male: Female:	
No of patients screened for MUS			
No of patients recruited			
No of patients allocated			
No of patients evaluated			
No of dropouts			
Reasons for dropouts			
Number of protocol violations			
Definition of MUS [1] Clinical interview [2] Standardised questionnaire Please circle all that applies and list all			
Status of patient at recruitment Any treatment for any comorbidities If treated: Please state What treatment Duration			
Adverse event? Yes/No *If Yes please state*			

Observational study characteristics (**please circle where appropriate**)	
Sample size	
Number of excluded patients	
Recruitment method	
Type of observational study	Cohort studies (prospective/retrospective) Case-control studies/nested case-control Cross-sectional studies
Are group comparable	Yes/No If No, please specify
Any confounders?	Yes/No If No, please specify
Analysis	
Drop outs stated	Yes/No If Yes:# in each group

Outcome details

The following table have been copied for every relevant outcome assessed (please fill out fields only where applicable)

Outcome assessed (**please state where relevant**)	
Definition of each outcome	
Time of assessment of each outcome (post MUS)	
Timing of assessment	
Length of follow up for each outcome	
Method of measurement	
No of patients evaluated for each outcome, as stated above	

Methodological quality summary for observational studies					
Reviewer/Date:			Checked by:		
Contents (please refer to tables below for guidance	Yes	Partly	No	Unsure	Comments
Study participation					
Study attrition					
Measurement of prognostic factors					
Measurement and controlling for confounding variables					
Measurement of outcomes					
Analysis approach					
Summarised validity	Low risk of bias		Moderate risk of bias		High risk of bias
Remarks:					

Prevalence rates of MUS

Supplementary table 4: Estimated prevalence rates of MUS in high users of healthcare

Study	Diagnostic criteria	Definition of high user	Prevalence in high users, n (%)	Prevalence among comparator, n (%)	OR/RR – High user v/s non-high user	Mean (SD) – High User	Mean (SD) – Non- High User	95% (CI); p-value
Burton et al[33]	Clinical assessment in secondary care	At least 3 referrals from primary to secondary care in the past 5 years (top 10%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Ferrari et al[34]	The Diagnostic Criteria for Psychosomatic Research (DCPR)	50 patients with the highest numbers of GP attendances in the previous year	14%	2%	OR: 9.33 (1.12-77.2)	Not reported	Not reported	Not reported
	DCPR diagnosis of functional somatic symptoms secondary to persistent psychiatric disorder		70%	18%	OR: 10.63 (4.15-27.25)	Not Reported	Not reported	Not reported
Gili et al[35]	SCAN diagnosis of somatoform disorder according to ICD-10 code	12+ visits to primary care centre in the previous year, excluding nursing, emergency, obstetric, home visits and those for bureaucratic purposes	17.3%	3.4%	Unadjusted OR: 7.6 (2.6-13.1) Adjusted OR: 3.4 (1.3-8.7)	Not reported	Not reported	P<0.001
	GHQ-28 somatisation subscale		1.74%	1.07%	**Unadjusted OR: 1.93 (0.34-19.7)*	Not reported	Not reported	P=0.414
Haas et al[36]	SCL-90-R score of 63+ on somatisation subscale	Adults aged 55+ who exceeded the mean number of inpatient and outpatient visits in the past year	56.5%	Not reported	Not reported	Mean(SD): Male: 0.88+/-0.43 Female: 1.18+/-0.76	0.36 +/-0.42	Not reported
Hansen et al[37]	SCAN diagnosis of somatoform disorder according to ICD-10	Top 20% of healthcare users in terms of number of admissions per year (>0.7)	Not reported	Not reported	OR: 6.46 (2.05-20.32)	Not reported	Not reported	Not reported
	Whitley index score of 3+ for somatisation		Not reported	Not reported	OR: 1.45 (1.18-1.77)	Not reported	Not reported	Not reported
Jacob et al[38]	Clinical diagnosis in medical records	5+ attendances to A&E in the previous year	45%	Not reported	Not reported	Not reported	Not reported	Not reported
Jyvasjarvi et al[39]	SCL-36 score of 8+ on somatisation subscale	Those who made 8+ visits to the GP in 1994	28.6%	16.0%	Unadjusted OR: 2.1 (1.04-4.1)	Not reported	Not reported	P=0.027

Study	Diagnostic criteria	Definition of high user	Prevalence in high users, n (%)	Prevalence among comparator, n (%)	OR/RR – High user v/s non-high user	Mean (SD) – High User	Mean (SD) – Non- High User	95% (CI); p-value
Jyvasjarvi et al[40]	Mean SCL-36 somatisation score	Those who made 8+ visits to the GP in 1994	Not reported	Not reported	Not reported	M: 20.9+/-6.8 F: 18.7+/-5.3	M: 15.5 +/- 4.7 F: 17.0 +/- 5.4	M: <0.001 F= 0.061
Karlsson et al[41]	DIS provided diagnosis of somatisation according to DSM-III-R criteria	11+ visits to GP in previous year	20.9%	Not reported	Not reported	Not reported	Not reported	Not reported
	Escobar et al's definition of abridged somatisation		73%	Not reported	Not reported	Not reported	Not reported	Not reported
Katon et al[42]	DIS provided diagnosis of somatisation according to DSM-III-R criteria	Top 10% of number of ambulatory healthcare visits for age-sex group in the previous year	20.20%	Not reported	Not reported	8.7 +/-5.6	Not reported	Not reported
Little et al[43]	Somatic symptom inventory, no clear cut-off provided, only presents ORs for different scores 6+ 3-5 1-2 0	5+ visits to primary care doctor or nurse in the last year (top 25%)	 26% 29% 27% 18%	 11% 22% 33% 34%	 1.62 (1.08-2.42) 1.48 (1.04-2.09) 1.15 (0.81-1.62) Not reported	Not reported	Not reported	Not reported
Mc Gorm et al[44]	Operationalised criteria for MUS by case notes review: 1.The final diagnosis suggests doubt surrounding the cause of symptom. 2. The final diagnosis is a recognized medically unexplained (functional) syndrome. 3. The investigations performed were normal or, if abnormal, was felt by the specialist to be an incidental finding or unlikely to account for the severity of the presenting symptom.	Patients with more than 3 GP referrals over the last 5 years	Male 24% Female 76%	Male (39%); Female (61%)	OR for those with 5-6 visits=1.86 (1.16-2.99) OR for those with 7+ visits= 2.11 (1.06-4.18)	Not reported	Not reported	Not reported

Study	Diagnostic criteria	Definition of high user	Prevalence in high users, n (%)	Prevalence among comparator, n (%)	OR/RR – High user v/s non-high user	Mean (SD) – High User	Mean (SD) – Non- High User	95% (CI); p-value
Miranda et al[45]	The National Institute of Mental Health Diagnostic Interview schedule equivalent to DSM III criteria of somatoform disorder	Did not provide a clear definition, how high users were defined. Medical records were reviewed in the 12 months to determine number of visits outpatients	Not reported	Not reported	Not reported	Not reported	Not reported	P=0.009 R Statistics (0.012)
Norton et al[46]	PHQ-9 was used which meets the DSM-IV diagnostic algorithms for somatoform disorder.	Frequent attenders described as the top 10% of patient with the highest number of self-reported visits in the last 6 months	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Patel et al[47]	Somatoform disorder defined as a structured clinical interview for DSM-IV and abridged criteria for somatisation disorder	30 or more GP or practice nurse consultations in 2 years	53%	6%	Unadjusted OR: 17 (4.4-146.1)	Not reported	Not reported	P<0.001
Portegijs et al[48]	DSM III criteria	High users defined as those who had at least 12 consultations with a GP in the previous 3 years	58%	29%	RR 2.0 (1.1-3.6)	Not reported	Not reported	p=0.0009
Reid et al[49]	MUS was determined a priori – patients with 2 or more unexplained episodes extracted from medical records	Top 5% of all outpatient appointments over a 3 year period	By age group <46=63.9%; ≥46=22%	By age group <46=45.2% ≥46=54.8%	**Unadjusted OR aged (<46 years): 2.15 (1.15-4.06)* **Unadjusted OR aged (≥46 years): 0.46 (0.25-0.87)*	Not reported	Not reported	*Aged (<46 years): P=0.009* *Aged (≥46 years): P=0.009*
Schmitz et al[50]	Composite International Diagnostic Interview (M-CIDI, World Health Organization 1997) for DSM-IV disorders by clinical interviewers	Patients above the 90th percentile associated with the use of outpatient department in the 12 months	By gender – Male=4.6% Female=8.3%	By gender – Male=2.9% Female=6.7%	**Unadjusted OR male: 1.73 (0.65-3.95)* **Unadjusted OR female: 1.29 (0.75-2.11)*	Not reported	Not reported	*Male: P=0.179* *Female: P=0.306*

Study	Diagnostic criteria	Definition of high user	Prevalence in high users, n (%)	Prevalence among comparator, n (%)	OR/RR – High user v/s non-high user	Mean (SD) – High User	Mean (SD) – Non- High User	95% (CI); p-value
Schneider et al[51]	PHQ-15 which matches the DSM IV diagnostic algorithm for somatoform disorder	Patients with more than 11 practice visits or referrals in the last 12 months	55.9%	15.8%	*Unadjusted OR: 6.75 (5.44-8.38)*	Not reported	Not reported	P<0.001
Smith et al[52]	DSMIII criteria and confirmed by the diagnostic interview schedule were included	Mean healthcare charges and hospital days	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Smith et al[53]	Physician assessment to determine somatisation	Having 6 or more visits (65th percentile) were defined as high users.	1995=61.2% 1996=17.8% 1997=13.1%	Not reported	Not reported	Not reported	Not reported	Not reported
Smits et al[54]	MUS determined by the International Classification of Primary Care (ICPC) code	Frequent attenders were defined as those patients whose attendance rate ranked nearest to the top 10th centile of their sex and age group	25.3%	6.8%	**Unadjusted OR: 4.6 (3.6-5.9)*	Not reported	Not reported	*P<0.001*
Taylor et al[55]	GP assessment based on a rating sheet to ascertain MUS and the brief symptoms inventory somatic score	The brief symptoms inventory was used to categorised unexplained symptoms	Not reported	Not reported	Not reported	19.58+/5.96	Not reported	Not reported
van den Bussche et al[56]	Diagnosis using the ICD-10 code F45 for somatoform disorder	Frequent attenders [≥50 contacts or ≥10 visits to different practices	Not reported	Not reported	RR 2.33 (2.20-2.50)	Not reported	Not reported	Not reported
Williams et al[57]	Schedules for Clinical Assessment in Neuropsychiatry	Patients had to have 7 or more visits to the emergency department in the last 12 months	1 (2.9%)	7 (3.8%)	**Unadjusted OR: 0.73 (0.01-6.04)*	Not reported	Not reported	*P=0.776*

* Indicates where odds ratios were not reported but calculated by the reviewers using the number of events in the high user and non-high user groups