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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<br>Reference lists of any recent review article<br>Eligible manuscript identified by database search |
| Participants | Adult aged ≥18 years<br>High user of healthcare<br>Accrue high healthcare costs<br>Presence of MUS |
| Comparator | Non-high cost and non-high users of healthcare |
| Outcome | Prevalence of MUS<br>Patient characteristics and context associated with high service usage/costs among patients with MUS<br>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

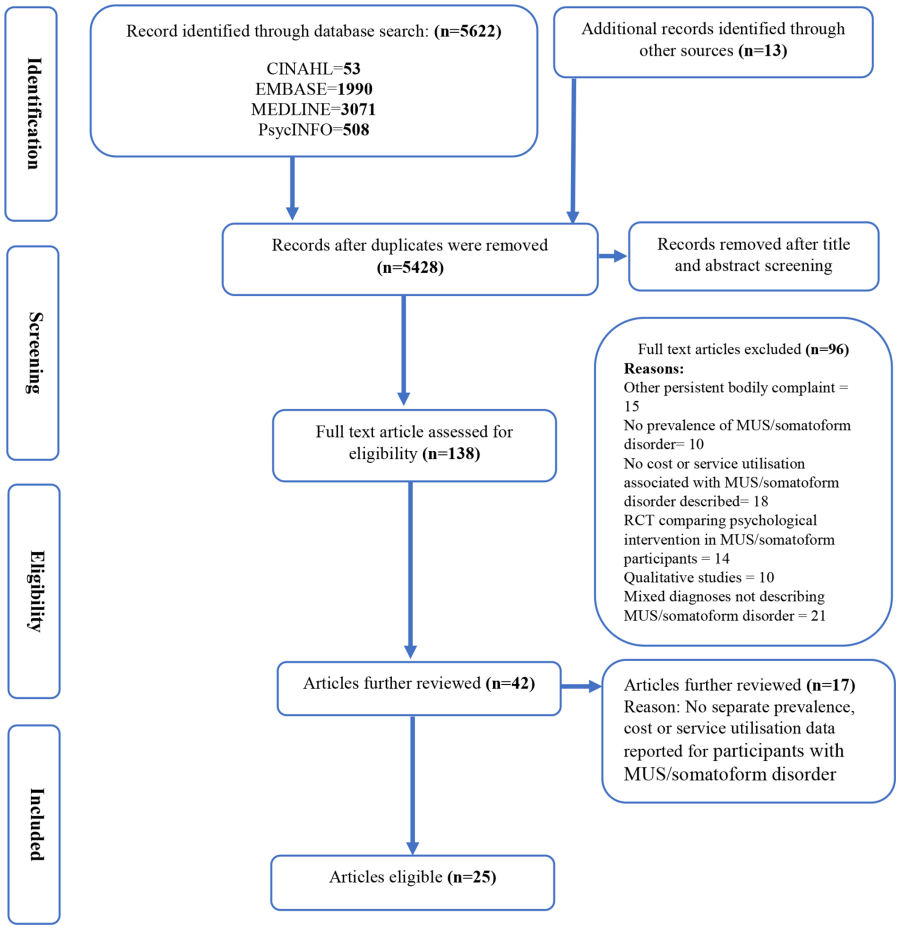


**Figure 1** PRISMA flow diagram of the study selection process. MUS, medically unexplained symptoms; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, randomised controlled trial.

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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