

# Prevalence of medically unexplained symptoms in adults who are high users of health care services

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# BMJ Open Prevalence of medically unexplained symptoms in adults who are high users of health care services: a systematic review and meta-analysis protocol

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## ABSTRACT

**Introduction** Medically unexplained symptoms (MUS) are common in primary-care and secondary-care settings. Persistent symptoms of MUS are associated with a variety of poor outcomes including increased disability, poor quality of life and high healthcare costs. The aim of this systematic review is to review the relevant literature to determine the prevalence of MUS in patients who are high users of healthcare and/or who accrue high healthcare costs.

**Methods and analysis** This review will include studies with cases that are either high users of general healthcare or are patients who accrue high healthcare costs, aged ≥18 years and where a recognised measure of MUS, either a standardised clinical interview or questionnaire, was employed. The following citation databases MEDLINE, PsycINFO, EMBASE, CINAHL, PROSPERO and the Cochrane library will be systematically searched from inception to 30 June 2018. The Cochrane library was included because of the significant proportion of non-observational studies currently published in the database. The prevalence of MUS and associated disorders along with the costs or use of healthcare associated with the presence of MUS will be estimated with 95% CI. If possible, study results will be pooled into a meta-analysis. However, if heterogeneity is high, data analysis will be presented descriptively.

**Ethics and dissemination** Ethical approval is not required for this systematic review since only data from existing studies will be used. Results of this review will be disseminated in peer-reviewed publications and at national and international conferences.

**PROSPERO registration number** CRD42018100388

## INTRODUCTION

Medically unexplained symptoms (MUS) is a general term which refers to physical symptoms that cannot be fully explained by observable pathology or known/recognised pathological mechanisms. Such symptoms can affect any part of the body and can range from minor occasional problems to severe and persistent symptoms resulting in functionally impaired states. At the more severe end, the MUS spectrum includes syndromes

## Strengths and limitations of this study

- To reduce bias, this review is not restricted to the English language or by publication date.
- A wide range of medical databases and study types will be used to identify potential papers for inclusion.
- A broad search strategy with a wide spectrum of search terms, including healthcare cost/utilisation, frequent attenders, Medically unexplained symptoms and healthcare settings, will be used.
- Study selection, data extraction and quality assessment will be conducted by two reviewers independently.
- We aim to conduct a meta-analysis. However, if sufficient number of studies are not available or where there is high heterogeneity between studies, a narrative summary of the included studies will be presented in the final review.

comprising multiple, chronic and disabling MUS.

One of the most common definitions of MUS is where a patient experiences physical symptoms 'whereby any disease or problem with the body cannot be found that would otherwise account for the symptoms'.<sup>1</sup> However, there is no completely satisfactory definition for MUS, as the area is conceptually and diagnostically challenging. The preferred, recent term is persistent physical symptoms.<sup>2</sup> Terms other than MUS have often been used, such as abridged somatisation disorder or multisomatoform disorder. These terms have predominantly been used for research purposes, to capture patients with moderate MUS, who may not meet the psychiatric diagnostic criteria.<sup>3</sup>

It is estimated that MUS accounts for approximately 20% of new consultations in primary care,<sup>4 5</sup> 52% of new referrals in secondary care<sup>6</sup> and 20%–25% of all frequent attenders at medical clinics.<sup>7 8</sup> Patients with MUS are commonly referred for multiple investigations and assessments with little



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benefit, so are needlessly costly for healthcare systems<sup>9–11</sup> and account for approximately 10% of the total National Health Service (NHS) expenditure for the working-age adult population 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.<sup>12</sup> 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 will aim 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).
- ▶ 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 AND DESIGN

### Population

This review will include studies where cases are adults who are high users of general healthcare or have high general healthcare costs, and have MUS. We will include ‘patients who accrue high healthcare costs’, ‘high users’, ‘distressed high users or users of care’, ‘frequent attenders in primary care’, ‘frequent attenders at the emergency department’.

Existing strings from databases such as the Cochrane database will be searched for additional search terms as appropriate. All cases will be adults aged 18 years or more. In studies where a proportion of participants is less than 18 years old, the mean or median age (in years) and a description of the distribution (SD, range or IQR range) will be provided. If these are not reported, the authors may be contacted to provide raw data for these to be calculated.

In all studies, a recognised measure of the presence of MUS should have been used. This could involve using any of the following: a standardised research interview (eg, the Structured Clinical Interview for Mental Disorders<sup>13 14</sup> to generate a diagnosis of a somatoform disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III<sup>15</sup>, DSM-IV-R<sup>16</sup>, DSM V<sup>17</sup>, International Classification of Diseases (ICD)-9<sup>18</sup>, ICD-10<sup>19</sup> or other relevant diagnostic systems; 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,<sup>20</sup> the Bradford somatic inventory,<sup>21</sup> or component subscales of validated standardised instruments for the assessment of general psychopathology or general health status, such as the Patient Health Questionnaire-15<sup>22</sup> or an assessment which generated a recognised symptom grouping

of MUS developed for research purposes (eg, abridged somatisation disorder,<sup>23</sup> multisomatoform disorder,<sup>24</sup> bodily distress disorder<sup>25</sup> and complex somatic symptom disorder.<sup>26</sup> Studies focusing on high use of mental health services, or specific medical sub-specialties, for example, oncology or obstetrics, will be excluded.

### Study design

This systematic review will consider observational studies including:

- ▶ Cohort studies – retrospective and prospective.
- ▶ Case-control and nested case-control.
- ▶ Cross-sectional studies.

Included studies will be published in either peer-reviewed scientific journals or Cochrane libraries. Single case studies and randomised controlled trials will be excluded.

### Search strategy

#### Search

An optimal search strategy has been developed to retrieve relevant articles which focus on the following key terms: medically unexplained symptoms (and all the associated diagnoses and research terms), high cost of healthcare, high healthcare use, frequent attenders, primary care, secondary care and emergency department. A detailed search strategy in Medline can be found in online supplementary appendix 1. The following citation databases Medline, PsycINFO, Embase, CINAHL, PROSPERO and Cochrane library will be searched from inception to 31 December 2018. The reference lists of any recent review articles and from any other eligible manuscript identified by the above search will be hand-searched. There will be no language restriction, if studies in a language other than English are included in the review. Internet sites such as google translate may be used to translate blocks of texts from various languages into English. Furthermore, international colleagues/students from the Universities of Birmingham, Leeds and Manchester can provide support in translating non-English articles. Additionally, authors of non-English articles may be requested to assist with data translation.

### Preparing for eligibility screening

Before the screening can commence, search results identified by the outlined databases will be assembled into a library and organised by database using the Endnote reference management tool. Duplicates will be identified and removed at this stage.

### Study selection

Two reviewers will independently screen and identify studies by reading titles and abstracts. Both reviewers will then select articles for full-text screening and independently apply eligibility criteria to select the appropriate articles for the review. Any disagreement over the eligibility of any study will be resolved through discussion with a third reviewer. An inclusion criteria checklist (table 1) has been developed based on study eligibility

**Table 1** Review eligibility criteria checklist

	<b>Cohort studies (retrospective and prospective)</b> <b>Case-control and nested case-control studies</b> <b>Study design Cross-sectional studies</b>
Study characteristics	Full articles Reference lists of any recent review article Eligible manuscript identified by the database search
Participants	Adult aged $\geq 18$ years High user of healthcare Accrue high healthcare costs Presence of Medically unexplained symptoms (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

criteria to ensure that studies are interpreted and classified appropriately. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) flow diagram will be provided to describe the included and excluded studies along with the reasons for exclusion. This review will be conducted according to the PRISMA-P reporting guidelines.<sup>27</sup>

### Quality assessment

Two reviewers will carry out the quality assessment of each selected article independently to reduce bias. Any difference in opinion will be resolved by further discussion/consensus or by involving a third reviewer. Study quality will be assessed focusing on sampling strategy, validated method to establish outcome, attrition and analytical method employed. All selected articles will be judged using a modified form adapted from the Ottawa-Newcastle Scale,<sup>28</sup> to assess the quality of the cohort, case-control and cross-sectional studies. Online supplementary appendix 2 shows the stages and domains of this modified tool. Risk of bias will be presented in accordance with the Cochrane Collaboration recommendations.<sup>29</sup> Risk of bias will not be displayed as a composite score; instead a risk of bias of 'yes' indicating high risk, 'no', low risk and 'unclear' will be provided to assess each domain. A narrative summary of the quality for each study will be provided in a table. A critical appraisal of the study quality describing the impact of the quality of each study on the results will be discussed. A sensitivity analysis will be conducted to assess the effect of including or excluding poor quality studies on the main findings.

### Data extraction

Two reviewers will independently screen and identify studies by reading titles and abstracts. Both reviewers will then select articles for full-text screening and independently apply eligibility criteria to select the appropriate articles for the review. Any disagreement over the eligibility of a study will be resolved through discussions with a third reviewer. Finally, both reviewers will independently extract data. For missing data, authors will be contacted for clarification. An Excel spreadsheet will be used to manage data extraction. A data extraction form (online supplementary appendix 3) will be designed based on the Hayden *et al* framework.<sup>30</sup> This form will be developed iteratively and pilot-tested on known papers independently by two reviewers. The form will be designed to focus on population, comparator, outcome and study design.

### Outcomes

The outcomes of this review will be categorised as follows:

- ▶ Primary outcome: prevalence of MUS.
- ▶ Secondary outcome: magnitude of cost or use of healthcare associated with the presence of MUS.

### Data analysis and synthesis

The outcomes of interest are the prevalence of MUS and cost or use of healthcare associated with the presence of:

1. MUS in patients who accrue high healthcare costs/high use populations alone.
2. MUS in patients who accrue high healthcare costs/high use populations in comparison with a relevant population (eg, general patient population or low cost/low use population).

Prevalence rates and standard errors will be extracted or calculated from the available data. If appropriate, cohort, case-control and cross-sectional studies will be grouped separately and pooled estimates of the prevalence rates with 95% CI will be calculated using STATA V.13.1 (STATA Corp). The analysis of the magnitude of healthcare utilisation and costs will be reported based on the definition of high users or patients who accrue high healthcare costs described by the included studies. To determine the cost or use of healthcare associated with the presence of MUS, the difference between groups (eg, cost/use of healthcare associated with MUS versus other relevant mental or physical conditions) will be extracted, where possible. Standardised mean difference with accompanying 95% CI and median OR of costs or healthcare utilisation will be extracted or calculated from the data provided. For studies reporting implementation of an intervention, changes in costs and healthcare utilisation before and after the intervention will be extracted and reported where available. Subgroup analyses of the outcome data may be performed if studies report, for example, clinical diagnosis of MUS based on ICD or DSM versus symptoms of MUS, setting (primary care, emergency department and secondary physical healthcare) or by age group. This will allow the prevalence of MUS,

costs and healthcare utilisation associated with MUS to be compared across these groups. Depending on the level of heterogeneity both fixed and random effect models will be used as summary effect measures. To assess the robustness of the meta-analysis and interpretation of the pooled results, the quality criteria of the studies entered in the meta-analysis will be considered. Therefore, separate sensitivity analyses may be conducted with at least the following assumptions: representative sampling strategy, adequate response rate and studies using both valid and standardised assessment and clinical interview to ascertain somatoform disorders/MUS. The level of heterogeneity across studies will be assessed using the Cochrane Q-test and the I<sup>2</sup>- statistical test with 95% CI. Publication bias and small sample bias will be assessed using the inverted funnel plot technique and the Egger statistics. The Grading of Recommendations Assessment, Development and Evaluation framework will be used to assess the quality of evidence for each outcome of interest described above across studies. Furthermore, inconsistency/imprecision, risk of bias including publication bias and applicability of the results based on the study population will also be rated when making judgement about the quality of evidence presented in the included studies.<sup>31</sup> If heterogeneity is high between studies, a narrative summary of the outcome of the selected studies will be presented in the final review.

#### Patient and public involvement statement

Patients and the public were not invited to contribute to the writing or editing of this systematic review protocol. 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.

#### DISCUSSION

This systematic review will aim 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. Strength and limitations identified in the literature will be highlighted and described in the review. Strength of observational data include large sample sizes, the potential to observe extended follow-up, frequency of attendance and healthcare cost associated with MUS likely to be representative of the population at risk. Limitations may include quality of the data extracted which may be inadequate to allow data to be combined in a meta-analysis. To overcome this problem, a narrative summary of the findings will be presented. The search criteria, keywords and Medical Subject Headings terms were reviewed and refined with the support of an experienced librarian. The team identified the most appropriate medical database(s) based on the review question. Two reviewers will conduct data extraction and screening independently employing a data extraction form which has been reviewed and

pretested. Additionally, this review is not limited to the English language and study date, and relevant papers will be translated to English for assessment. To the best of our knowledge, no existing review addresses our research question. However, if a review addressing a similar question is published, it will be incorporated in this review and, if feasible, added to the meta-analysis.

#### Implications of results

This systematic review will provide a reliable estimate of the prevalence of MUS in adults aged ≥18 years who are high users of healthcare services and/or accrue high healthcare costs. Furthermore, an updated and quantifiable estimate of the costs attributed to the presence of MUS will be presented if sufficient evidence is available. One of the main premises of delivering psychological treatments for MUS is that such interventions may reduce healthcare costs in addition to improving patient outcomes. This review will inform policy makers, clinicians and researchers of the costs related to MUS in 'high users of healthcare', enabling more targeted interventions to be developed. Such interventions may focus on patients with MUS but, in addition, address factors related to healthcare use, and be of sufficient intensity to impact on healthcare behaviour. Additionally, the systematic search and the evidence gathered may inform future policy directions by quantifying the problem more accurately than has been done before and highlighting the degree to which limited healthcare resources are being used effectively for a vulnerable and needy group of people.

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**Contributors** FJ and OCL developed the search strategy. FJ drafted the manuscript and registered the protocol. EG and AB were involved in the design of the review and provided continuous feedback on the manuscript. FJ will be first reviewer and OCL will be second reviewer. All authors read and approved the manuscript.

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