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The prevalence of common mental health disorders in adults who are high or costly users of health care services: A systematic review and meta-analysis

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Abstract

Introduction: In all health care settings, a small proportion of patients account for a large proportion of health care use and associated high health care costs. Common mental health disorders, such as anxiety and depression, especially when unmanaged, are a source of frequent primary and secondary care appointments. The aim of this systematic review is to determine the prevalence and magnitude of depression and anxiety in adults who are high users of physical health care services and who accrue high health care costs.

Methods and Analysis: This review will include any studies where patients are high users of primary and secondary health care services and/or accrue high health care costs. We will focus on patients who are over the age of 18 and whose level of anxiety and/or depression has been evaluated with a standardized questionnaire or clinical interview. The review will include eligible studies indexed in MEDLINE, PsychINFO, EMBASE, CINAHL, PROSPERO, Cochrane Library from inception to June 2018. We will estimate the prevalence of anxiety or depression in these populations, the level of health care use and health care costs, together with the associated 95% confidence intervals. We will provide a narrative description of results; a meta-analysis will be pursued if sufficient homogeneous studies are identified.

Ethics and dissemination: This systematic review will use data from existing studies, hence no ethical approvals are required. Findings will be disseminated in peer-reviewed publications and in national and international conferences.

PROSPERO Registration number: CRD42018102628

Strengths and Limitations:

1. This systematic review is not restricted to studies published in English or by publication date.
2. Potential studies will be identified through a wide range of databases.
3. The search strategy uses a broad terminology to ensure a comprehensive inclusion of studies focusing on distressed high users in general health care settings and the associated magnitude of health care use and costs.
4. Study screening, selection, data extraction, and study quality evaluation will be pursued independently by two reviewers.
5. We will provide a narrative summary of findings and describe limitations of prior research in this area. If possible we will conduct a meta-analysis. However, this may not be possible if we find a limited number of studies or a high heterogeneity in outcomes.

Introduction

Across health care systems, a small proportion of the patient population accounts for a large proportion of health care use and cost [1]. These findings have consistently emerged from studies of general practice (GP) attendances [1–4], inpatient length of stay [5,6], outpatient appointments [7,8], A&E services [9–12]. In primary care, approximately 5% of ‘frequent attenders’ can account for up to 50% of all consultations [13]. In secondary care, 5% of the top users consume 30-40% of the resources [14]. This has been estimated to amount to more than $30 billion of total annual health care expenditures [13–17].

It has been suggested that approximately 50% of high users of health care in the primary and secondary care settings have significant mental health problems, either alone or, in addition, to physical health needs, and have been termed ‘distressed high users’ [15,18]. High use of health care services have been associated with a variety of different mental health problems including multiple psychiatric diagnoses [8,19,20], long histories of psychological ill health/social adversity [2,10,21,22], history of childhood abuse or neglect [23], or addictions [24]. Despite this evidence, the prevalence of anxiety/depression in these populations and the costs associated with their medical use are unclear. The aim of this review is to determine the prevalence of anxiety and/or depression in patients who are high users of health care services, or accrue high health care costs, and to estimate the frequency and costs of their medical use.

Aims:

This systematic review will aim to: (1) determine the prevalence of anxiety and/or depression in adults over 18 years old, who are high users of health care or accrue high health care costs; (2) determine the magnitude of health care use and the magnitude of health care costs associated with the presence of anxiety and/or depression.

Methods and design

Population: This review will include studies focusing on adults aged ≥18 years, who are high users of health care services or accrue high health care costs, and whose level of depression or anxiety have been evaluated through standardized questionnaires or clinical interviews. We will focus on patients seen in general health care settings, such as primary, secondary, tertiary care, A&E/emergency departments. We will not include studies with populations seen in the context of psychiatric or mental health services for a primary diagnosis of a psychiatric condition (i.e. psychosis, schizophrenia) given that the aim is to estimate the prevalence of anxiety/depression in general health care. While we will include patients seen in the general hospital, accident and emergency, and primary care settings, we will not include specific medical or surgical specialties, or specific disease conditions (e.g. palliative care, obstetrics, genetics, pharmacology, transplant, surgery, neurodegenerative diseases, oral and maxillofacial, dentistry, nephrology, infectious diseases, virology (including HIV/AIDS-related studies), nephrology, physiotherapy, infectious diseases, and cosmetic surgery).

Interventions: We will include studies evaluating naturalistic general health service interventions for emotional distress in high need, high cost frequent attenders in any of the health care settings detailed above. We will exclude clinical trials given their selective selection criteria. We will also exclude studies that only focus on comparing the costs or performance of screening, diagnosis, instrument development, vaccination, development/implementation or evaluation of new health care services not related to high cost/frequent health care users.

Comparators: We will include studies comparing groups of patients with an average cost/use of health care versus those defined as high cost/frequent users. We will also include studies comparing patients with and without high levels of anxiety/depression.

Outcomes: The primary outcome will be the prevalence of anxiety/depression in high users of general health care services. The secondary outcome will focus on the costs associated with the high use of health care services in this population.

Study designs: We will include both retrospective and prospective cohort studies, case-control, and cross-sectional studies as well as any previous meta-analyses related to our topic. We will exclude case studies and randomized controlled trials.

Search Strategy

Study search: We will screen the five databases that are most likely to include studies focusing on our outcomes of interest: Medline, Embase, CINAHL, PROSPERO, and the Cochrane Library, from inception to June 2018. The search will include all languages; translations will be pursued through by co-authors, where possible, or through colleagues in our international universities. The search will be restricted to studies with adults over the age of 18. We will also hand search the references of recent reviews. For each databases queried, we will divide our search strategy into three parts. Search terms within the first part will aim to identify studies pertaining to all healthcare settings of interest (see search terms for Medline in Appendix 1). The second part will focus on terms related to high cost or high/frequent use of health care services. The final part will focus our search on studies evaluating anxiety/depression.

Eligibility screening: Studies identified in all the databases will be organised using the EndNote reference management software. Duplicates will be identified and removed.

Study selection

Titles and abstracts will be screened independently by two reviewers. Remaining full-text articles will be further screened and evaluated for their eligibility. Any disagreement over eligibility will be resolved through discussions with a third reviewer. We have developed a comprehensive inclusion criteria checklist (Table 1) to ensure consistency in the review process and adherence to the PRIMSA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[25]; we will also provide a PRISMA flow-chart depicting the study selection and inclusion process.

Table 1: Eligibility criteria checklist based on the PRISMA guidelines

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 the database search
Participants	Adult aged (≥18 years) High user of health care Accrue high health care costs Presence of anxiety/depression
Comparator	Non-high cost and non-high users of health care
Outcome	Prevalence of anxiety/depression Patients characteristics and context associated with high service usage/costs among patients with anxiety/depression Magnitude of cost or use of health care associated with the presence of anxiety/depression

Quality assessment

Quality assessment will be carried out independently by two reviewers through an adapted Newcastle-Ottawa Scale [26] (NOS, Appendix 2). Assessment of study quality will include sampling methods, sample size, method of outcome evaluation (i.e. evaluation of anxiety/depression through one or multiple methods), participant attrition, and analytical method. The adapted NOS quality assessment form will first be piloted on known papers to ascertain its feasibility. Opinion differences will be resolved by consensus or by involving a third reviewer, as necessary. Risk of bias will be evaluated commensurate with the recommendations of the Cochrane Collaboration [27]. It will be reported in a categorical format, with ‘yes’ indicating high risk ‘no’ low risk or ‘unclear’ for each pre-defined domain.

We will provide a descriptive account of the study quality and risk of bias for each study included in our review. If a meta-analysis were to be pursued, low quality studies will be removed during the sensitivity analyses.

Data extraction

Following the selection of relevant full-text articles, two reviewers will independently extract relevant information in a data extraction form. The latter will be designed based on Hayden et al.'s framework [28] (Appendix 3); it will be developed iteratively and first piloted on known papers, by two reviewers, before performing the data extraction for all studies.

Data analysis and synthesis

The primary outcome will be the prevalence of anxiety/depression in high and/or costly users of health care services. The secondary outcomes will include a quantification of the use and costs associated with these patients. Data analysis will employ descriptive statistics and narrative synthesis, as appropriate. Quantitative summaries will include standardised mean differences with associated 95% confidence intervals, and median odds, depending on the primary data. If sufficient studies using comparable outcomes are available, we will pursue a meta-analysis. Where possible subgroup analyses will be pursued based on expected study differences related to: 1) type of outcome measurement for depression/anxiety (clinical interview versus self-report questionnaires) and 2) healthcare setting (primary care, secondary care, emergency department). Sensitivity analyses will include effect size estimates of prevalence and costs in high and low quality studies. Heterogeneity will be estimated using the Q-test and I^2 test with 95% confidence intervals and publication bias will be estimated through Egger's test.

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 and magnitude of depression and anxiety in adults who are high users of physical health care services and who accrue high health care

Discussion

The purpose of this systematic review is to estimate the prevalence of anxiety/depression in people who are frequent, high cost users of general health care services, and then to generate the estimated level of health care use and associated costs in different medical settings.

While evidence is available suggesting that a small percentage of the population accrues the highest costs, it is unclear to date to what extent the costs and usage may be due to un-diagnosed or un-managed common mental health problems. By examining the information available to date we aim to describe the strengths and limitations of prior literature in terms of sample sizes, methodological approaches, instruments employed, methods of evaluating frequency of attendances, and health care costs.

To our knowledge there are no similar comprehensive reviews that address the same question and we expect the studies we identify to be heterogeneous. However, to be able to offer a complete image, we will employ a highly robust literature search, using both key words and MeSH terms, refined with the support of local librarians. Other strengths of this review are that it includes all studies published in any language without a time limit, and the independent study identification, selection, and data extraction pursued by two reviewers.

Implications of results

The results of this systematic review will provide an estimate of the prevalence of common mental health disorders in high users of health care services, while also providing an estimate of costs associated with the higher use. This critical review of available evidence may highlight the need for more robust research in this area. It may also reveal an unmet need in the diagnosis and appropriate management of anxiety/depression in populations routinely seen in general health care settings. This review will provide an overview of the burden associated with a prevalence of poorly identified or managed anxiety/depression in patients who are routinely managed in physical health care settings. Hence, it could suggest the type of integrated, collaborative services, or management methods that may be needed for people who suffer from either acute or chronic physical illnesses, who are routinely managed in the physical health care setting, but also have a mental health concerns.

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Abbreviations

PROSPERO: Prospective Registering of Systematic Reviews; CINAHL: Cumulative Index for Nursing and Allied Health Literature; CI: Confidence Interval; GRADE: Grading of recommendation assessment, development and evaluation; OR: Odds Ratio; NHS: National Health Service; GP: General Practitioner; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; NOS: The Newcastle – Ottawa Scale; ICD: International Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders.

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Contributors:

OL and FJ developed the search strategy. OL 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. OL will be first reviewer and FJ will be second reviewer. All authors read and approved the manuscript.

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Competing Interest:

The authors declare that they have no competing interests.

Provenance and Peer Review:

Not commissioned; externally peer reviewed.

Data Sharing and Statement:

There are no unpublished data as this is a systematic review

Appendix 1:

Electronic search strategy in Medline used to conduct a comprehensive literature search.

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

Part 2: Cost/service utilisation	
41	high cost.mp.
42	high cost$.ti,ab,de.
43	high?cost$.ti,ab,de.
44	(high adj5 cost$).ti,ab,de.
45	frequent cost.mp.
46	frequent cost$.ti,ab,de.
47	(frequent adj5 cost$).ti,ab,de.
48	high expenditure.mp.
49	high expenditure.ti,ab,de.
50	(high adj5 expenditure).ti,ab,de.
51	high expense.mp.
52	high expense.ti,ab,de.
53	(high adj5 expense).ti,ab,de.
54	frequent user.mp.
55	frequent user.ti,ab,de.
56	(frequent adj5 user).ti,ab,de.
57	high user.mp.
58	high user.ti,ab,de.
59	(high adj5 user).ti,ab,de.
60	high utiliser.mp.
61	high utiliser$.ti,ab,de.
62	high utilizer.mp.
63	high utilizer$.ti,ab,de.
64	(high adj5 utiliser$).ti,ab,de.
65	(high adj5 utilizer$).ti,ab,de.
66	frequent utiliser.mp.
67	frequent utilizer.mp.
68	frequent utilizer$.ti,ab,de.
69	frequent utiliser$.ti,ab,de.
70	(frequent adj5 utilizer$).ti,ab,de.
71	(frequent adj5 utiliser$).ti,ab,de.
72	high utilisation.mp.
73	high utilization.mp.
74	high utilization.ti,ab,de.
75	high utilisation.ti,ab,de.
76	(high adj5 utilization).ti,ab,de.
77	(high adj5 utilisation).ti,ab,de.
78	frequent utilisation.mp.
79	frequent utilization.mp.
80	frequent utilisation.ti,ab,de.
81	frequent utilization.ti,ab,de.
82	(frequent adj5 utilisation).ti,ab,de.

83	(frequent adj5 utilization).ti,ab,de.
84	high need.mp.
85	high need.ti,ab,de.
86	(high adj5 need).ti,ab,de.
87	high attend.mp.
88	high attend$.ti,ab,de.
89	(high adj5 attend$).ti,ab,de.
90	superutilizer.mp.
91	superutilizer.ti,ab,de.
92	exp health expenditures/
93	exp patient acceptance of health care/
94	exp health care costs/
95	exp health services accessibility/
96	exp cost benefit analysis/
97	exp practice patterns physicians/
98	exp efficiency organizational/
99	exp health services misuse/
100	exp patient care team/
101	exp case management/
102	exp office visits/
103	exp referral/
Part 3: Anxiety/Depression terms	
104	exp anxiety/
105	(anxiety adj5 disorder$).tw
106	exp panic disorder/
107	(panic adj5 disorder$).tw
108	panic.tw
109	(panic adj5 attack$).tw
110	fear.tw
111	exp depression/
112	(depressive adj5 disorder$).tw

Appendix 2:

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, anxiety/depression) [2] Was inclusion/exclusion assessed using valid and reliable measures? (for example, clinical interview to ascertain anxiety/depression 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 anxiety/depression	
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 anxiety/depression) ➢ 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 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 drop-outs/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? (i.e. mean change)	
Analytical methods appropriate	[1] Was the type of analysis appropriate for the type 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)	

Appendix 3

Data extraction form adapted from Hayden and colleagues Framework

Abbreviation

GP	General Practitioner
OR	Odd ratios
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 **NB:** Please answer YES if anxiety/depression are 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 anxiety/depression [2] Patients characteristics and context associated with high service usage/costs among patients with anxiety/depression [3] Magnitude of cost or use of healthcare associated with the presence of anxiety/depression		
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 with established psychiatric condition
Intervention	[1] Testing of any intervention [2] Screening
Comparator	Studies without non-high cost/non-high users of health care
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 anxiety/depression [2] Patients characteristics and context associated with high service usage/costs among patients with anxiety/depression [3] Magnitude of cost or use of healthcare associated with the presence of anxiety/depression 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 anxiety/depression			
No of patients recruited			

No of patients allocated			
No of patients evaluated			
No of drop-outs			
Reasons for drop-outs			
Number of protocol violations			
Definition of anxiety/depression [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 groups 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	
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:					

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	3
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	N/A

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

The prevalence of common mental health disorders in adults who are high or costly users of health care services: Protocol for a systematic review and meta-analysis

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The prevalence of common mental health disorders in adults who are high or costly users of health care services: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: In all health care settings, a small proportion of patients account for a large level of health care use and associated high health care costs. Depression and anxiety are common co-morbidities in patients who are high users of care. The aims of this systematic review are to: (1) estimate the prevalence of anxiety/depression in adults who are high users of general physical health care services and/or who accrue high health care costs (2) estimate the magnitude of health care use associated with the presence of anxiety/depression.

Methods and Analysis: This review will include any studies where patients are high users of primary, secondary, or emergency health care services and/or accrue high health care costs. We will focus on patients who are over the age of 18 whose degree of anxiety/depression has been evaluated with a standardised questionnaire or by a clinical interview generating a diagnosis according to international diagnostic criteria. The review will include eligible studies indexed in MEDLINE, PsychINFO, EMBASE, CINAHL, PROSPERO, Cochrane Library from inception to 1st April 2019. We will estimate the prevalence of anxiety/depression in these populations, and the magnitude of use associated with anxiety/depression. We will provide a narrative description of findings and factors that may influence them. A meta-analysis may be pursued if the degree of heterogeneity across studies is acceptable.

Ethics and dissemination: This systematic review will use data from existing studies, hence no ethical approvals are required. Findings will be disseminated in a peer-reviewed publication and at relevant academic meetings.

PROSPERO Registration number: CRD42018102628

STRENGTHS AND LIMITATIONS

1. This systematic review includes both studies of high health care use and/or high health care costs.
2. It includes studies of primary, secondary care, and emergency departments.
3. It focuses upon studies that have specifically recorded the presence of depression and/or anxiety in the high cost/high use population studied.
4. A narrative summary of findings and sources of variation based on a comprehensive data extraction framework will be provided with relevant subgroup analyses based upon: country, type of health care system, location of study (primary, secondary care, emergency department, or total health care), and way of recording depression/anxiety.
5. A meta-analysis may not be feasible given a likely high level of heterogeneity in outcome definitions and measurements.

INTRODUCTION

The cost of health care in developed countries has continued to grow over recent years and the current projected trajectories of growth are unsustainable [1]. This situation is particularly severe in the United States (US), where the cost of health care is nearly twice that of most other developed countries [1,2]. Across health care systems, a small proportion of patients account for a large proportion of health care use and cost [3]. These findings have consistently emerged from studies of general practice (GP) attendances [4], inpatient length of stay [5,6], outpatient appointments [7], and emergency department (ED) services [8–10]. In primary care, approximately 10% of 'frequent attenders' account for up to 39% of all consultations [11]. In the US approximately 5% of patients account for about 50% of all US health care spending [12].

It has been suggested that approximately 50% of high users of health care in primary and secondary care have significant mental health problems, either alone or, in addition to physical health needs, and have been termed 'distressed high users' [13]. High use of health care services has been associated with a variety of mental health problems including multiple psychiatric diagnoses [14,15], long histories of psychological ill health [16,17], history of childhood abuse or neglect [18], or addictions [19].

A recent systematic review of the general characteristics of high-cost patients found a high prevalence of multiple chronic conditions amongst the patient population [20]. Mental health problems were also common but varied according to the health care system. In US Medicaid, the prevalence of mental illness ranged from 30-75%, whereas in US Medicare, the prevalence was between 10-25%. There were, however, no details as to the nature of mental health problems experienced by these high-cost patients, as data were grouped under a broad category of mental and behavioral disorders. One of the main findings of the review was a notable difference in characteristics and utilization across payers and countries.

Several methods have been studied to try to improve the care of high-cost or high-use patients in the hope of reducing excessive or unnecessary health care use, but efforts to date have had mixed results [21,22]. Evidence suggests that effectiveness and efficiency of care improves when interventions are targeted to those who are most likely to benefit [23,24]. Specific interventions for treating depression and anxiety in people with co-morbid physical health problems have shown promising results [25,26] but have not been targeted at high-cost patients with co-morbid depression/anxiety.

Improved recognition of the association of depression and anxiety with high health care use and costs will enable treatments that have already been developed for depression/anxiety in physical disease, to be evaluated in this high need/high cost group. Although there has been a general call for better integration of physical and mental health services, the treatment and management of co-morbid depression/anxiety in chronic physical disease remains poorly managed [27].

Our aim is to estimate the prevalence of anxiety/depression in adults who are high users of health care or accrue high health care costs and where possible to estimate the magnitude of use associated with anxiety/depression. Segmentation analysis has been suggested as a method to identify homogeneous groups of patients with similar characteristics, needs, and behaviors in order to personalize treatment and policy [28]. We are specifically interested in depression and anxiety, as opposed to all mental health problems, as interventions have already been developed to treat depression/anxiety when associated with physical disease. Such interventions could be used to target a subgroup of high use/cost patients with the potential to improve their health and reduce health care use. Other forms of mental illness require other treatment approaches.

Aims

This systematic review will aim to: (1) estimate the prevalence of anxiety and/or depression in patients who are high users of health care or accrue high health care costs; (2) determine the magnitude of health care use associated with the presence of anxiety and/or depression.

METHODS AND DESIGN

Population

This review will include studies focusing on adults aged ≥18 years, who are high users of health care services or accrue high health care costs, and whose level of depression/anxiety have been evaluated through standardised questionnaires or clinical interviews. We include studies conducted in primary, secondary care, and emergency departments (ED) and across all health care systems. We will not include studies with populations seen in the context of psychiatric or mental health services for a primary diagnosis of a psychiatric condition (i.e. psychosis, schizophrenia) as the aim is to estimate the prevalence of anxiety/depression among high users of general physical health care services. We will not include specific medical specialties/illnesses associated with more frequent or costly health care use due to the nature of the condition or type of specialty (e.g. surgery, paediatrics, palliative care, obstetrics, transplant, neurodegenerative diseases, oral and maxillofacial, dentistry, nephrology, infectious diseases, virology and HIV/AIDS studies, physiotherapy, and cosmetic surgery).

We have focused on general hospital and primary care services, to ensure the review is relevant to as wide a population as possible. There is great variability in the way costs, health care use, and depression/anxiety have been recorded in the literature. To add studies on individual disease conditions or specialities would considerably inflate the variability within the population of this review.

For studies of high-cost patients, we will include studies that have defined high cost patients as being in the top 1st, 5th, 10th and 20th percentiles of the patient population [20]. For studies involving high use of health care, we will include studies that have either used similar percentiles to describe high use (i.e. 1st, 5th, 10th or 20th) or have used a recognised definition of high or frequent use. For ED, we will use the definition of 4 or more attendances per annum [29]. For primary care, we will use the definition of 10 or more attendances per year [30] or the top 10% of consulters [31].

The review includes studies of costs and health care use. However, resource use and costs are sensitive to variability both within and between countries, due to aspects such as local prices or aspects of service organization and delivery. This limits the generalizability and transferability of estimates of cost and health care across settings. We will not attempt to combine costs or health use in the analyses across studies. The prevalence of depression or anxiety will be compared across studies. To determine the magnitude of health care use associated with depression/anxiety in high-use/high-cost patients, we will calculate the odds ratios for health care used by depressed and non-depressed individuals.

Interventions

We will not include randomised controlled trials, due to their selective nature. We will include cohort studies of naturalistic changes in health service delivery e.g. implementation of a new integrated care pathway across a geographical region, where external validity is likely to be high.

Comparators

We will include studies where anxiety/depression is described in groups of patients considered ‘high/frequent users’ and/or ‘high cost users’ versus non-high cost and non-high users of healthcare services. We will include studies where high health care use/costs are compared between patients with anxiety/depression versus study patients without anxiety/depression.

Outcomes

The primary outcome is the prevalence of anxiety/depression in high/frequent and/or costly users of general health care services. The secondary outcome is the magnitude of health care use and costs associated with anxiety/depression. Studies including a diverse range of standardised assessments and metrics for anxiety/depression will be eligible. We will extract and report the prevalence of anxiety/depression based upon the type of assessments used. For standardised, validated, self-report measures, this will be in the form of caseness. For clinical interviews, this will be in the form of a clinical diagnosis.

Study designs

We will include retrospective and prospective cohort studies, case-control, nested case-control, and cross-sectional studies. We will exclude case studies, randomised controlled trials, and qualitative studies.

Search Strategy

We will screen the five databases that are most likely to include studies focusing on our outcomes of interest: MEDLINE, PsychINFO, EMBASE, CINAHL, PROSPERO, Cochrane Library, from inception to 1st April 2019. We will hand-search reference lists of relevant reviews/meta-analyses. For each database our search strategy has three parts (see search terms for Medline in Appendix 1). Search terms within the first part will identify studies pertaining to general health care settings of interest. The second part will focus on terms related to high cost or high/frequent use of health care services. The final part will focus the search on studies evaluating anxiety/depression. This strategy ensures we identify all studies (1) conducted across general health care settings such as primary, secondary care, and emergency departments; (2) which include measurements of health care use and/or costs; (3) and assess anxiety/depression. We will not be able to include studies that do not quantify either health care use OR costs and studies that do not quantify anxiety/depression. This strategy ensures we include cohort studies describing the characteristics of high use and/or cost patients and case-control studies where (1) anxiety/depression is compared between high and low use and/or costs, as defined by the respective study or where (2) health care use/costs is compared between patients with high and low levels of anxiety/depression, as defined by the study.

The strategy was developed in collaboration with experts in these fields and experienced librarians at the Universities of Birmingham and Manchester, to ensure it yields appropriate studies. We will include studies in all languages; translations will be pursued either by co-authors or by international colleagues/students in the Universities of Birmingham, Leeds, and Manchester. The search will be restricted to studies with adults over the age of 18.

Eligibility screening

Eligible studies identified in all the databases will be organised using the EndNote reference management software. Duplicates will be identified and removed before screening titles and abstracts.

Study selection

Titles and abstracts will be screened independently by two reviewers. Remaining full-text articles will be further screened and evaluated for their eligibility using the adapted Hayden et al. framework [32] (Appendix 2). Any disagreement over eligibility will be resolved through discussions with a third reviewer. The inclusion criteria checklist (Table 1 and Appendix 2) ensures consistency in the review process and adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]; we will provide a PRISMA flow-chart depicting the study selection and inclusion/exclusion process.

Table 1: Inclusion criteria checklist based on the PRISMA guidelines

Study designs	Cohort studies (Retrospective and Prospective) Case-control and nested case-control studies Cross-sectional studies
Participants	Adult aged ≥18 years High user of health care Accrue high health care costs Assessment of anxiety/depression
Comparators	Non-high cost and non-high users of health care Frequent/high cost users without depression/anxiety
Outcomes	Prevalence of anxiety/depression in high users of health care and/or high cost patients Magnitude of cost or use of health care associated with the presence of anxiety/depression

Quality assessment

The quality of the included studies will first be ensured through the robustness of our database search and the careful title, abstract, and full-text screening of relevant studies, carried out independently by two reviewers using the forms in Appendix 2. We will only include studies reporting on high OR costly users of health care where anxiety/depression is also assessed. All full-text studies meeting the eligibility criteria will undergo a quality assessment carried out independently by two reviewers through an adapted Newcastle-Ottawa Scale [34] (NOS, Appendix 3). Assessment of study quality will include sampling method, sample size, adequacy of description of study population, attrition, method of outcome evaluation (e.g. methods for recording costs/use; type of anxiety/depression measurements, whether they are validated for the setting, etc.), analytical method, and consideration of confounders/covariates. The adapted NOS quality assessment form will first be piloted on known papers to ascertain its feasibility. Opinion differences will be resolved by consensus or by involving a third reviewer. Risk of bias will be evaluated commensurate with the recommendations of the Cochrane Collaboration [35]. It will be reported in a categorical format, with 'yes' indicating high risk 'no' low risk or 'unclear' for each pre-defined domain. We will describe the study quality and risk of bias for each study included in our review. For both low- and high-quality studies we will provide a narrative description of definitions and measurements of costs and health care use, and prevalence of anxiety /depression used across health care settings, regions, and patient populations. If a meta-analysis can be pursued, we will run a sensitivity analysis to explore if outcomes change when removing low quality studies. Through sensitivity analyses we will also specifically explore the effects of excluding studies which have used non-validated measures of depression/anxiety in medically ill populations.

Data extraction

Following the selection of relevant full-text articles and quality assessment, two reviewers will independently extract relevant information in a data extraction form designed based on Hayden et al.'s framework [32] (Appendix 2); it will be developed iteratively and first piloted on five known papers, by two reviewers, before performing the data extraction for all studies.

The data extraction form focuses on the study design, population, comparator, and outcome. It will include: year and country of study, type of health care system, criteria used to define high use or high costs, method used to record depression/anxiety (self-report measure validated or non-validated, clinical interview), prevalence of depression and anxiety, health care use, and costs and associated ranges, the methods used to evaluate these, health care settings (e.g. primary, secondary or ED or total health care), the odds ratios of use of health care by depressed/anxious patients compared with non-depressed/anxious patients, patient characteristics (e.g. co-morbidities, whether anxiety/depression is managed).

DATA ANALYSIS AND SYNTHESIS

The primary outcome is the prevalence of anxiety and/or depression in patients who are high and/or costly users of health care services. Prevalence rates with any dispersion metrics will be extracted or calculated from the data available. If enough studies are available for quantitative summaries we will offer weighted estimates of prevalence within relevant subgroups related to populations, comparators, study designs, measurement types, and geographical regions. Pooled prevalence estimates with 95% confidence intervals will be calculated using SPSS version 25 (IBM Corp, Armonk, NY, USA).

The secondary outcome is the magnitude of health care use associated with the presence of anxiety/depression. We are not attempting to pool or calculate costs or health use across studies. We will only be able to determine the magnitude of health care use associated with depression/anxiety in relation to studies that have specifically calculated or estimated these. This will be studies where high health care use/costs are compared between patients with anxiety/depression versus patients without anxiety/depression. Odds ratios and 95% confidence intervals will be extracted from studies presenting the number of health care contacts (e.g. ED attendances or GP contacts or number of hospital admissions) by subjects with and without depression.

We expect both the prevalence of depression/anxiety to be available from studies evaluating high use/cost populations alone, or in studies comparing high use/cost patients to general patient populations or populations with low use/cost. Data analysis will result in quantitative and narrative summaries, as appropriate.

For both outcomes, subgroups will be explored based on potential differences related to: 1) country, 2) type of healthcare system, 3) medical settings (e.g. primary care, ED, inpatients, outpatients, etc.), 4) metrics used to evaluate health use/costs (e.g. attendances, hospital admissions, etc.).

We will use random-effects models to describe the prevalence of depression/anxiety high use or high cost populations. This is because it is implausible that the underlying study-specific prevalence of depression (i.e. the prevalence that would be observed were a study of infinite size) is the same for each study. Prevalence is likely to vary from study to study according to factors, both measured and unmeasured, that differ between them [36].

We will use the inverse variance method of DerSimonian and Laird to estimate between-study heterogeneity in underlying depression prevalence and the I-squared measure which represents the proportion of total variance attributable to this heterogeneity [37,38]. The I-squared measure gives the percentage of variability in the effect estimate that is due to heterogeneity rather than to chance. Suggested thresholds for the interpretations of the I-squared measure are as follows: less than 40% indicates there is no problem with heterogeneity, 30% to 60% indicates moderate problems, 60% to 90% a substantial problem, and 75% and over a considerable problem [38]. We will use the threshold of less than 40%.

Egger's statistics with 95% confidence intervals and associated funnel plot will depict potential publication or small bias related to our main outcome summaries and/or within subgroups [39]. Egger's test is based on the Galbraith plot which is a plot of difference over standard error against one over standard error. Egger suggests that a regression of study difference over standard error on 1/standard error be undertaken to test the null hypothesis that the intercept is equal to zero. If Egger's test is significant ($p<.05$), it means that the funnel plot is asymmetric and that smaller studies with smaller precision show larger effects sizes, suggesting bias.

Sensitivity analyses will be pursued at minimum on high/low quality studies and on the use of un-validated standardised questionnaires, and use of structured clinical interviews. If enough studies are available, other factors that could influence our observed findings will be explored (e.g. sample size). Tabular and narrative descriptions will be offered for the studies which cannot be pooled into quantitative summaries due to differing metrics.

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 was informed by the lack of prior systematic reviews or meta-analyses exploring the outcomes of interest: prevalence of anxiety/depression in high/costly health care users and the magnitude of health care use associated with anxiety/depression across adult populations in any general medical settings.

DISCUSSION

The purpose of this systematic review is to estimate the prevalence of anxiety/depression in people who are frequent, high cost users of general health care services, and then, if possible, to estimate the level of health care use associated with the presence of anxiety/depression. While evidence is available suggesting that a small percentage of the population accrues high percentage of healthcare/costs, it is unclear to date to what extent the costs and use may be due to the presence of common mental health problems (depression/anxiety). By examining the information available to date we aim to describe the prevalence of anxiety/depression in people who are high/costly health care users, and where possible the magnitude of use and costs associated with these two common mental health problems.

Our review will build upon the recent systematic review by Wammes and colleagues [20] that described the characteristics of high-cost patients and found that a high prevalence of high cost patients had associated mental health disorders. This review will specifically focus upon depression/anxiety and include both studies of cost and health care use. It will also provide information about the prevalence of depression/anxiety in different health care settings, including primary care and ED. There is trade-off between diagnostic accuracy versus size of study. Our results will complement those of Wammes and colleagues [20], and increase our understanding of the role of depression/anxiety in driving health care use and costs.

Strengths of this review are that it focuses upon common mental health problems, includes all studies without a time limit, includes both studies of health care cost and health care use, and includes general health care settings, including primary and secondary care. Additional strengths are the inclusion of studies published in any language and the independent study identification, selection, and data extraction pursued by two independent reviewers.

IMPLICATIONS OF RESULTS

The results of this systematic review will provide an estimate of the prevalence of common mental health disorders in high users of health care services, while also providing an estimate of the magnitude of use associated with depression/anxiety. It will enable treatments, such as the collaborative care model, that have already been developed for the treatment of depression/anxiety in the physically ill, to be evaluated in high-cost patients with co-morbid depression/anxiety resulting in a more personalised approach to both treatment and policy.

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CONTRIBUTORS

OL and FJ developed the search strategy. OL 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. OL will be first reviewer and FJ will be second reviewer. All authors read and approved the manuscript.

COMPETING INTEREST

The authors declare that they have no competing interests.

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DATA SHARING AND STATEMENT

There are no unpublished data as this is a systematic review.

PATIENT CONSENT

Patient consent is not applicable as this is a protocol for a systematic review/meta-analysis.

ETHICS AND DISSEMINATION

As this systematic review will use data from existing studies no ethical approvals are warranted; the results will be published in a peer-reviewed publication and presented at relevant academic meetings.

Appendix 1:

Electronic search strategy in Medline used to conduct a comprehensive literature search.

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

Part 2: Cost/service utilisation	
41	high cost.mp.
42	high cost$.ti,ab,de.
43	high?cost$.ti,ab,de.
44	(high adj5 cost$).ti,ab,de.
45	frequent cost.mp.
46	frequent cost$.ti,ab,de.
47	(frequent adj5 cost$).ti,ab,de.
48	high expenditure.mp.
49	high expenditure.ti,ab,de.
50	(high adj5 expenditure).ti,ab,de.
51	high expense.mp.
52	high expense.ti,ab,de.
53	(high adj5 expense).ti,ab,de.
54	frequent user.mp.
55	frequent user.ti,ab,de.
56	(frequent adj5 user).ti,ab,de.
57	high user.mp.
58	high user.ti,ab,de.
59	(high adj5 user).ti,ab,de.
60	high utiliser.mp.
61	high utiliser$.ti,ab,de.
62	high utilizer.mp.
63	high utilizer$.ti,ab,de.
64	(high adj5 utiliser$).ti,ab,de.
65	(high adj5 utilizer$).ti,ab,de.
66	frequent utiliser.mp.
67	frequent utilizer.mp.
68	frequent utilizer$.ti,ab,de.
69	frequent utiliser$.ti,ab,de.
70	(frequent adj5 utilizer$).ti,ab,de.
71	(frequent adj5 utiliser$).ti,ab,de.
72	high utilisation.mp.
73	high utilization.mp.
74	high utilization.ti,ab,de.
75	high utilisation.ti,ab,de.
76	(high adj5 utilization).ti,ab,de.
77	(high adj5 utilisation).ti,ab,de.
78	frequent utilisation.mp.
79	frequent utilization.mp.
80	frequent utilisation.ti,ab,de.
81	frequent utilization.ti,ab,de.
82	(frequent adj5 utilisation).ti,ab,de.

83	(frequent adj5 utilization).ti,ab,de.
84	high need.mp.
85	high need.ti,ab,de.
86	(high adj5 need).ti,ab,de.
87	high attend.mp.
88	high attend$.ti,ab,de.
89	(high adj5 attend$).ti,ab,de.
90	superutilizer.mp.
91	superutilizer.ti,ab,de.
92	exp health expenditures/
93	exp patient acceptance of health care/
94	exp health care costs/
95	exp health services accessibility/
96	exp cost benefit analysis/
97	exp practice patterns physicians/
98	exp efficiency organizational/
99	exp health services misuse/
100	exp patient care team/
101	exp case management/
102	exp office visits/
103	exp referral/
Part 3: Anxiety/Depression terms	
104	exp anxiety/
105	(anxiety adj5 disorder$).tw
106	exp panic disorder/
107	(panic adj5 disorder$).tw
108	panic.tw
109	(panic adj5 attack$).tw
110	fear.tw
111	exp depression/
112	(depressive adj5 disorder$).tw

Appendix 2 - Data extraction form adapted from the framework of Hayden et al.

Eligibility criteria for the title and abstract screening phase

Inclusion criteria

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] Adults aged ≥ 18 years [2] Patients are high users of health care [2] Patients accrue high health care costs Including: high cost patients, high users, distressed high users/utilisers of care, frequent attenders in primary care, secondary care, frequent attenders at an emergency department **NB:** Please answer YES if patients with anxiety/depression are a subgroup; please answer YES if mixed age population.	Yes No Unclear	
Comparators		
[1] Comparison group includes non-high use OR non-high cost patients [2] Comparison group includes frequent/high users without anxiety/depression	Yes No Unclear	
Outcome		
Did the study report any of the following outcomes: [1] Prevalence of anxiety/depression in high users/high cost patients [2] Odds Ratio of use of care between depressed/anxious vs non-depressed/anxious participants	Yes No Unclear	
Final decision (please tick)	Include Exclude Unclear	

Exclusion criteria

Reasons for exclusion of study from review (please circle where appropriate)	
Study design	[1] Clinical trial [2] Case study [3] Qualitative study
Population	Age: <18 All specific medical specialties/illnesses including: [1] Paediatric patients [2] Palliative care [3] Obstetrics [4] Transplant [5] Neurodegenerative disease [6] Oral, maxillofacial, dentistry [7] Nephrology [8] Infectious diseases [9] Virology and HIV/AIDS [10] Physiotherapy [11] Cosmetic surgery

	[12] Psychiatry/mental health services [13] Specific diseases e.g. diabetes, cardiovascular
Intervention	[1] Randomised clinical trial [2] Interventions in populations who are not high use/cost [3] Screening/diagnosis/treatment evaluations
Comparator	Studies without non-high cost/non-high users of health care
Outcomes	Relevant outcomes not assessed: [1] No anxiety/depression assessment [2] No assessment of health use OR cost
Other	Duplicate publication Other (explain)

Eligibility criteria for Full Text	
Satisfaction of eligibility criteria above	Yes No Unclear
Cost studies will include patients either in the top 1%, 5% 10% and 20% of most costly patients.	**Yes** **No** **Unclear**
Studies of general health care use will include patients in the top 1%, 5%, 10% or 20% of health care use.	**Yes** **No** **Unclear**
Studies in primary care will either include patients with 10 or more visits per year or those patients in the top 10% of use	**Yes** **No** **Unlcear**
Studies of ED will include patients with at least 4 visits per annum.	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/Exclude without listing/Exclude with listing Other – please specify			
Notes				

Data extraction template for full-text articles

General study characteristics	
Location of study Please specify country, type of health care system, health care setting (primary/secondary care/ED/all settings)	
Study aims	Reported/Not reported
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 (standard deviation):#
Outcome definition	[1] Anxiety or depression or both Median (range):# Mean (standard deviation):# [2] Health care use Median (range):# Mean (standard deviation):# [3] Health care cost Median (range):# Mean (standard deviation):#
Outcome measurement	Did the study report measurements for any of the following outcomes: [1] Prevalence of anxiety/depression ➢ Specify measures of central tendency and variation) ➢ Specify instrument and range (e.g. PHQ-9, GAD-7, SCID, etc.) ➢ Is it self-report? ➢ Is it standardised? ➢ Is it validated to context? ➢ Is it a standardised clinical interview ➢ Is it a clinical interview with diagnosis according to recognised diagnostic system [2] Magnitude of cost or use of health care associated with the presence of anxiety/depression. Consider: ➢ Frequency and range of scheduled contacts in primary care, secondary care or ED ➢ Cost, range, of contacts in above settings ➢ Frequency and range of inpatient admissions ➢ Cost, range, currency of inpatient admissions
Covariates/Confounders considered (please detail)	[1] Did the study report measurements used to report: ➢ Patient characteristics and contexts associated with high service use/costs among patients with anxiety depression? *Please consider patient demographic (e.g. age, ethnicity, gender, homelessness) and clinical factors (e.g. anxiety/depression management, physical co-morbidities)*
Relationship between outcome and relevant covariates/confounders	Is the relationship statistically significant? Yes/No *If Yes:* OR/mean difference (95% confidence intervals):# *If No, offer reason:* Low powered or inconclusive study A true negative study

	Other reasons (please specify)
Power calculation	Yes/No/Not reported Calculated sample size:# Sample size achieved: Yes/No
Funding	Unclear Not reported Please state where reported
Conflict of interest statement	Yes/No/Not reported

Observational study characteristics	
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 groups comparable	Yes/No If No, please specify
Any confounders considered?	Yes/No If Yes, specify which If No, please specify
Analyses	
Drop-outs stated	Yes/No If Yes: number in each group

Patient characteristics			
Notes: Any relationship with outcomes? Yes/No/Not reported *If Yes,* please state statistical parameters and significance level where appropriate	Exposure (i.e. High use/cost)	Control (Low use/cost)	Comments
Number of patients			
Country			
Age mean/median (standard deviation/range)			
Ethnicity (Number, %)			
Sex (Number, %)	Male: Female:	Male: Female:	
Homelessness specified in study? Yes/No			
No of patients recruited			
No of patients allocated			
No of patients evaluated			
No of drop-outs			
Reasons for drop-out			
Definition of anxiety/depression in the groups:			

[1] Via standardised questionnaire (validated or not) semi-structured or clinical interview? *Please specify* [2] Definition of high/low ranges or diagnosis (yes/no) [3] Is anxiety/depression managed? Yes/No			
Clinical status at recruitment : [1] Comorbidities Yes/No *If yes, please state* Number:			
Adverse event? Yes/No *If Yes, please detail*			

Outcome details

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

Outcome assessed	
Definition of each outcome	
Time of assessment of each outcome	
Timing of assessment	
Length of follow up for each outcome	
Method of measurement	
No of patients evaluated for each outcome, as stated above	
Confounding variables were considered (e.g. age, gender, ethnicity, homelessness, physical co-morbidities, managed depression) *Please list all*	
How were the confounding variables controlled?	

Methodological quality summary					
Reviewer/Date:			Checked by:		
Contents (please refer to tables below for guidance	Yes	Partly	No	Unsure	Comments
Study participation					
Study attrition					
Measurement of outcome					
Analytical approach					
Specify confounding variables measurements (e.g. age, gender, ethnicity, homelessness, physical co-morbidities, managed depression)					

Specify method of controlling for confounding variables					
Summary	Low risk of bias		Moderate risk of bias		High risk of bias
Remarks:					

Appendix 3

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, anxiety/depression) [2] Was inclusion/exclusion assessed using valid and reliable measures? (for example, clinical interview to ascertain anxiety/depression 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 ➢ Homelessness (yes/no) ➢ Suitable definition of anxiety/depression	
Valid method for evaluating outcome	[1] Was there a definition provided for the key outcomes: ➢ Anxiety/depression caseness or diagnosis ➢ Health care use level and range ➢ Health care costs and range [2] Was there a method used to ascertain anxiety/depression clearly defined? ➢ Standardised questionnaires validated to the setting ➢ Standardised questionnaire not validated for the setting ➢ Clinical interview based on the ICD or DSM (version specified) ➢ Semi-structured research interview based on ICD or DSM version specified [3] Was a valid and reliable measure used to report outcomes? For example ➢ Frequency/range of health care use ➢ Mean/variation/currency of health care cost ➢ Clinical interview/Questionnaire score/variation	
Adequate follow-up period *(where applicable)*	[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 *(where applicable)*	[1] Were drop-out rates and reasons for drop-out similar across exposed and unexposed? [2] Were numbers of drop-outs/withdrawals documented at each time point?	
Analysis and control of confounders	[1] Does the study identify any confounders? [2] Does the study control for these confounders?	
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? (i.e. mean change)	
Analytical methods appropriate	[1] Was the type of analysis appropriate for the type of outcome data? For example:	

	- Continuous – Mixed model, ANCOVA - Categorical - Mixed model for categorical outcome - Dichotomous – Logistic regression [2] Was loss to follow-up accounted for in the analysis (e.g. through sensitivity analysis)	

Abbreviations

PROSPERO: Prospective Registering of Systematic Reviews; CINAHL: Cumulative Index for Nursing and Allied Health Literature; NHS: National Health Service; GP: General Practitioner; ED: Emergency Department; ANCOVA: Analysis of Covariance; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; NOS: The Newcastle – Ottawa Scale; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalised Anxiety Disorder Assessment-7; SCID: Structured Clinical Interview for DSM; ICD: International Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	3
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	N/A

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

The prevalence of common mental health disorders in adults who are high or costly users of health care services: Protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028295.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Jul-2019
Complete List of Authors:	Jadhakhan, Ferozkhan; University of Birmingham, Institute of Mental Health, School of Psychology, College of Life and Environmental Sciences; Birmingham and Solihull Mental Health NHS Foundation Trust, Research and Innovation Lindner, Oana; University of Leeds, Division of Psychological and Social Medicine, Leeds Institute of Health Sciences, School of Medicine, Level 10, Worsley Building, Clarendon Way, University of Leeds Blakemore, Amy; University of Manchester, Guthrie, Elspeth; University of Leeds Leeds Institute of Health Sciences, Psychological and Social Medicine
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health economics, Mental health, Emergency medicine, General practice / Family practice
Keywords:	Common Mental Health Disorders, Depression, Anxiety, Health Care Utilisation, High Cost, High Health Care Cost

The prevalence of common mental health disorders in adults who are high or costly users of health care services: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: In all health care settings, a small proportion of patients account for a large level of health care use and associated high health care costs. Depression and anxiety are common co-morbidities in patients who are high users of care. The aims of this systematic review are to: (1) estimate the prevalence of anxiety/depression in adults who are high users of general physical health care services and/or who accrue high health care costs (2) estimate the magnitude of health care use associated with the presence of anxiety/depression.

Methods and Analysis: This review will include any studies where patients are high users of primary, secondary, or emergency health care services and/or accrue high health care costs. This is the first systematic review to focus on patients who are over the age of 18 whose degree of anxiety/depression has been evaluated with a standardised questionnaire or by a clinical interview generating a diagnosis according to international diagnostic criteria. The review will include eligible studies indexed in MEDLINE, PsychINFO, EMBASE, CINAHL, PROSPERO, Cochrane Library from inception to 1st April 2019. We will estimate the prevalence of anxiety/depression in these populations, and the magnitude of use associated with anxiety/depression across various general physical health care settings. We will provide a narrative description of findings and factors that may influence them. A meta-analysis may be pursued if the degree of heterogeneity across studies is acceptable.

Ethics and dissemination: This systematic review will use data from existing studies, hence no ethical approvals are required. Findings will be disseminated in a peer-reviewed publication and at relevant academic meetings.

PROSPERO Registration number: CRD42018102628

STRENGTHS AND LIMITATIONS

1. This systematic review will include both studies of high health care use and/or high health care costs.
2. It will include studies undertaken in general physical health care settings - primary, secondary care, and emergency departments.
3. It will focus upon studies that have specifically recorded the presence of depression and/or anxiety in the high cost/high use population studied, using standardized questionnaires or clinical interviews leading to a clinical diagnosis.
4. We will provide a narrative summary of findings with sources of variation and bias based on a comprehensive data extraction framework, with relevant subgroup analyses and interpretations based upon: country, type of health care system, location of study (primary, secondary care, emergency department, or total health care), and way of recording depression/anxiety.
5. A meta-analysis may not be feasible given a likely high level of heterogeneity in outcome definitions and measurements.

INTRODUCTION

The cost of health care in developed countries has continued to grow over recent years and the current projected trajectories of growth are unsustainable [1]. This situation is particularly severe in the United States (US), where the cost of health care is nearly twice that of most other developed countries [1,2]. Across health care systems, a small proportion of patients account for a large proportion of health care use and cost [3]. These findings have consistently emerged from studies of general practice (GP) attendances [4], inpatient length of stay [5,6], outpatient appointments [7], and emergency department (ED) services [8–10]. In primary care, approximately 10% of 'frequent attenders' account for up to 39% of all consultations [11]. In the US approximately 5% of patients account for about 50% of all US health care spending [12].

It has been suggested that approximately 50% of high users of health care in primary and secondary care have significant mental health problems, either alone or, in addition to physical health needs, and have been termed 'distressed high users' [13]. High use of health care services has been associated with a variety of mental health problems including multiple psychiatric diagnoses [14,15], long histories of psychological ill health [16,17], history of childhood abuse or neglect [18], or addictions [19].

A recent systematic review of the general characteristics of high-cost patients found a high prevalence of multiple chronic conditions amongst this patient population [20]. Mental health problems were also common but varied according to the health care system. In US Medicaid, the prevalence of mental illness ranged from 30-75%, whereas in US Medicare, the prevalence was between 10-25%. One of the main findings of the review was that high-cost patients were more likely to have a mental health disorder. There were, however, no details as to the nature of mental health problems experienced by these high-cost patients, as data were grouped under a broad category of mental and behavioral disorders. This review will focus on patients with depression and anxiety disorders, as they are the most common form of mental disorder. We will focus upon studies where depression and anxiety are identified through standardized questionnaires or by clinical interviews leading to a clinical diagnosis. Our review will provide information about the prevalence of depression/anxiety in both high- and low-income countries and in different general physical health care settings, namely primary, secondary care, and ED.

Several methods have been studied to try to improve the care of high-cost or high-use patients in the hope of reducing excessive or unnecessary health care use, but efforts to date have had mixed results [21,22]. Evidence suggests that effectiveness and efficiency of care improves when interventions are targeted to those who are most likely to benefit [23,24]. Specific interventions for treating depression and anxiety in people with co-morbid physical health problems have shown promising results [25,26] but have not been targeted at high-cost patients with co-morbid depression/anxiety.

Improved recognition of the association of depression and anxiety with high health care use and costs will enable treatments that have already been developed for depression/anxiety in physical disease, to be evaluated in this high need/high cost group. Although there has been a general call for better integration of physical and mental health services, the treatment and management of co-morbid depression/anxiety in chronic physical disease remains poorly managed [27].

Our aim is to estimate the prevalence of anxiety/depression in adults who are high users of health care or accrue high health care costs and where possible to estimate the magnitude of use associated with anxiety/depression. Segmentation analysis has been suggested as a method to identify homogeneous groups of patients with similar characteristics, needs, and behaviors in order to personalize treatment and policy [28]. We are specifically interested in depression and anxiety, as opposed to all mental health problems, as interventions have already been developed to treat depression/anxiety when associated with physical disease. Such interventions could be used to target a subgroup of high use/cost patients with the potential to improve their health and reduce health care use. Other forms of mental illness require other treatment approaches.

Aims

This systematic review will aim to: (1) estimate the prevalence of anxiety and/or depression in patients who are high users of health care or accrue high health care costs; (2) determine the magnitude of health care use associated with the presence of anxiety and/or depression.

METHODS AND DESIGN

Population

This review will include studies focusing on adults aged ≥18 years, who are high users of health care services or accrue high health care costs, and whose level of depression/anxiety have been evaluated through standardised questionnaires or clinical interviews. We include studies conducted in general rather than specialist physical health services, namely primary, secondary care, and ED, across all health care systems. We will not include studies with populations seen in the context of psychiatric or mental health services for a primary diagnosis of a psychiatric condition (i.e. psychosis, schizophrenia) as the aim is to estimate the prevalence of anxiety/depression among high users of general physical health care services. We will not include specific medical specialties/illnesses associated with more frequent or costly health care use due to the nature of the condition or type of specialty (e.g. surgery, paediatrics, palliative care, obstetrics, transplant, neurodegenerative diseases, oral and maxillofacial, dentistry, nephrology, infectious diseases, virology and HIV/AIDS studies, physiotherapy, and cosmetic surgery).

We have focused on general hospital, ED, and primary care services to ensure the review is relevant to as wide a population as possible. There is great variability in the way costs, health care use, and depression/anxiety have been recorded in the literature. To add studies on individual disease conditions or specialities would considerably inflate the variability within the population of this review.

For studies of high-cost patients, we will include studies that have defined high cost patients as being in the top 1st, 5th, 10th and 20th percentiles of the patient population [20]. For studies involving high use of health care, we will include studies that have either used similar percentiles to describe high use (i.e. 1st, 5th, 10th or 20th) or have used a recognised definition of high or frequent use for the particular health care services. For ED, we will use the definition of 4 or more attendances per annum [29]. For primary care, we will use the definition of 10 or more attendances per year [30] or the top 10% of consulters [31].

The review will include studies reporting costs and health care use. However, resource use and costs are sensitive to variability both within and between countries, due to aspects such as local prices or aspects of service organization and delivery. This may limit the generalizability and transferability of estimates of cost and health care across settings. We will not attempt to combine costs or health use in the analyses across studies. The prevalence of depression or anxiety will be compared across studies. To determine the magnitude of health care use associated with depression/anxiety in high-use/high-cost patients, we will estimate the health care used by depressed and non-depressed individuals. If sufficient studies report similar effect measures (e.g. odds ratios, relative risk, incidence rate ratios) of the frequency of health care use in these patients [32], they will be combined in a meta-analysis, consistent with current recommendations [33–35]. Studies reporting different effect measures will not be combined, unless they can be transformed [34,35].

Interventions

We will not include randomised controlled trials, due to their selective nature. We will include cohort studies of naturalistic changes in health service delivery e.g. implementation of a new integrated care pathway across a geographical region, where external validity is likely to be high.

Comparators

We will include studies where anxiety/depression is described in groups of patients considered ‘high/frequent users’ and/or ‘high cost users’ versus non-high cost and non-high users of healthcare services. We will include studies where high health care use/costs are compared between patients with anxiety/depression versus study patients without anxiety/depression.

Outcomes

The primary outcome is the prevalence of anxiety/depression in high/frequent and/or costly users of general health care services. The secondary outcome is the magnitude of health care use and costs associated with anxiety/depression. Studies including a diverse range of standardised assessments and metrics for anxiety/depression will be eligible. We will extract and report the prevalence of anxiety/depression based upon the type of assessments used. For standardised, validated, self-report measures, this will be in the form of caseness. For clinical interviews, this will be in the form of a clinical diagnosis. Studies will be excluded if they do not meet our criteria for the assessment of anxiety or depression. A review concerning general mental health disorders has already been undertaken by Wammes et al [20].

Study designs

We will include retrospective and prospective cohort studies, case-control, nested case-control, and cross-sectional studies. We will exclude case studies, randomised controlled trials, and qualitative studies.

Search Strategy

We will screen the five databases that are most likely to include studies focusing on our outcomes of interest: MEDLINE, PsychINFO, EMBASE, CINAHL, PROSPERO, Cochrane Library, from inception to 1st April 2019. We will hand-search reference lists of relevant reviews/meta-analyses. For each database our search strategy has three parts (see search terms for Medline in Appendix 1). Search terms within the first part will identify studies pertaining to general health care settings of interest. The second part will focus on terms related to high cost or high/frequent use of health care services. The final part will focus the search on studies evaluating anxiety/depression. This strategy ensures we identify all studies (1) conducted across general health care settings such as primary, secondary care, and ED; (2) which include measurements of health care use and/or costs; (3) and assess anxiety/depression. We will not be able to include studies that do not quantify either health care use OR costs and studies that do not quantify anxiety/depression. This strategy ensures we include cohort studies describing the characteristics of high use and/or cost patients and case-control studies where (1) anxiety/depression is compared between high and low use and/or costs, as defined by the respective study or where (2) health care use/costs is compared between patients with high and low levels of anxiety/depression, as defined by the study.

The strategy was developed in collaboration with experts in these fields and experienced librarians at the Universities of Birmingham and Manchester, to ensure it yields appropriate studies. We will include studies in all languages; translations will be pursued either by co-authors or by international colleagues/students in the Universities of Birmingham, Leeds, and Manchester. The search will be restricted to studies with adults over the age of 18.

Eligibility screening

Eligible studies identified in all the databases will be organised using the EndNote reference management software. Duplicates will be identified and removed before screening titles and abstracts.

Study selection

Titles and abstracts will be screened independently by two reviewers. Remaining full-text articles will be further screened and evaluated for their eligibility using the adapted Hayden et al. framework [36] (Appendix 2). Any disagreement over eligibility will be resolved through discussions with a third reviewer. The inclusion criteria checklist (Table 1 and Appendix 2) ensures consistency in the review process and adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37]; we will provide a PRISMA flow-chart depicting the study selection and inclusion/exclusion process.

Table 1: Inclusion criteria checklist based on the PRISMA guidelines

Study designs	Cohort studies (Retrospective and Prospective) Case-control and nested case-control studies Cross-sectional studies
Participants	Adult aged ≥18 years High user of health care Accrue high health care costs Assessment of anxiety/depression
Comparators	Non-high cost and non-high users of health care Frequent/high cost users without depression/anxiety
Outcomes	Prevalence of anxiety/depression in high users of health care and/or high cost patients Magnitude of cost or use of health care associated with the presence of anxiety/depression

Quality assessment

The quality of the included studies will first be ensured through the robustness of our database search and the careful title, abstract, and full-text screening of relevant studies, carried out independently by two reviewers using the forms in Appendix 2. We will only include studies reporting on high OR costly users of health care where anxiety/depression is also assessed. All full-text studies meeting the eligibility criteria will undergo a quality assessment carried out independently by two reviewers through an adapted Newcastle-Ottawa Scale [38] (NOS, Appendix 3). Assessment of study quality will include sampling method, sample size, adequacy of description of study population, attrition, method of outcome evaluation (e.g. methods for recording costs/use; type of anxiety/depression measurements, whether they are validated for the setting, etc.), analytical method, and consideration of confounders/covariates. The adapted NOS quality assessment form will first be piloted on known papers to ascertain its feasibility. Opinion differences will be resolved by consensus or by involving a third reviewer. Risk of bias (including reporting bias) will be evaluated commensurate with recent recommendations for the narrative interpretation of variation in observational studies [34,35] and the recommendations of the Cochrane Collaboration [39,40]. Risk of bias will be reported in a categorical format, with 'yes' indicating high risk 'no' low risk or 'unclear' for each pre-defined domain. We will describe the study quality and risk of bias for each study included in our review. For both low- and high-quality studies we will provide a narrative description of definitions and measurements of costs and health care use, and prevalence of anxiety /depression used across health care settings, regions, and patient populations. If a meta-analysis can be pursued, we will run a sensitivity analysis to explore if outcomes change when removing low quality studies. Through sensitivity analyses we will also specifically explore the effects of excluding studies which have used non-validated measures of depression/anxiety in medically ill populations.

Data extraction

Following the selection of relevant full-text articles and quality assessment, two reviewers will independently extract relevant information in a data extraction form designed based on Hayden et al.'s framework [36] (Appendix 2); it will be developed iteratively and first piloted on five known papers, by two reviewers, before performing the data extraction for all studies.

The data extraction form focuses on the study design, population, comparator, and outcome. It will include: year and country of study, type of health care system, criteria used to define high use or high costs, method used to record depression/anxiety (self-report measure validated or non-validated, clinical interview), prevalence of depression and anxiety, health care use, costs, and associated ranges, the methods used to evaluate these, health care settings (e.g. primary, secondary or ED or total health care use/cost, if reported as general metrics), health care use and cost estimates for depressed/anxious patients compared with non-depressed/anxious patients, and patient characteristics (e.g. co-morbidities, whether anxiety/depression is managed). We will also record the presence and source of bias, including funding, given its potential association with reporting bias [39,40].

DATA ANALYSIS AND SYNTHESIS

The primary outcome is the prevalence of anxiety and/or depression in patients who are high and/or costly users of health care services. Prevalence rates with any dispersion metrics will be extracted or calculated from the data available. Where enough studies are available for quantitative summaries (minimum two studies [41]) we will offer weighted estimates of prevalence within relevant subgroups related to populations, comparators, study designs, measurement types, and geographical regions. Pooled prevalence estimates with 95% confidence intervals will be calculated using SPSS version 25 (IBM Corp, Armonk, NY, USA); where possible and warranted, estimate transformations and quantitative summaries will be pursued using R [33].

The secondary outcome is the magnitude of health care use associated with the presence of anxiety/depression. We are not attempting to pool or calculate costs or health use across studies. We will only be able to determine the magnitude of health care use associated with depression/anxiety in relation to studies that have specifically calculated or estimated these. This will be studies where high health care use/costs are compared between patients with anxiety/depression versus patients without anxiety/depression. Outcome metrics (including odds ratios, relative risk etc.) and 95% confidence intervals will be extracted from studies presenting the number of health care contacts (e.g. ED attendances or GP contacts or number of hospital admissions) by subjects with and without depression.

We expect both the prevalence of depression/anxiety to be available from studies evaluating high use/cost populations alone, or in studies comparing high use/cost patients to general patient populations or populations with low use/cost. Data analysis will result in quantitative and narrative summaries, as appropriate, based on current recommendations for the pooling of observational studies [34,35]. Whereas there is some published guidance on the number of studies necessary to ensure the power of the effect size estimates when pooling interventional studies [32,42], there are no similar clear, agreed guidelines on the number of studies necessary for an appropriately powered meta-analysis of observational studies. We will offer a quantitative summary for any number of studies (2>) if combining their outcomes is clinically meaningful, if they report the same effect metrics, or transformations are possible [34,35,41]. We will comment on these pooled results in light of clinical practice and research significance and potential statistical issues that may decrease the generalizability of the effect estimates (e.g. high level of heterogeneity, potential sources of bias). For both outcomes, subgroups will be explored quantitatively and narratively, as appropriate and depending on the type of effect estimates available, based on potential differences related to: 1) country, 2) type of healthcare system, 3) medical settings (e.g. primary, secondary care, ED, inpatients, outpatients, etc.), 4) metrics used to evaluate health use/costs (e.g. attendances, hospital admissions, etc.). For instance, we expect to find studies that may only focus on frequent attendance at ED, primary care outpatient visits, number of bed days in secondary care, or more generic attendance metrics across either of these health care settings. We will account for such differences in reporting, but we are not planning to compare outcomes across settings, just to record and estimate the magnitude of use/cost in each of these contexts.

We will use random-effects models to describe the prevalence of depression/anxiety high use or high cost populations. This is because it is implausible that the underlying study-specific prevalence of depression (i.e. the prevalence that would be observed were a study of infinite size) is the same for each study. Prevalence is likely to vary from study to study according to factors, both measured and unmeasured, that differ between them [43].

We will use the inverse variance method of DerSimonian and Laird to estimate between-study heterogeneity in underlying depression prevalence and the I-squared measure with associated 95% confidence intervals, which represents the proportion of total variance attributable to this heterogeneity [39,44]. The I-squared measure gives the percentage of variability in the effect estimate that is due to heterogeneity rather than to chance. A rough guide to the interpretation of the I-squared measure suggests that I-square < 40% indicates low to no problems with heterogeneity, 30% to 60% indicates moderate problems, 60% to 90% indicates significant problems, whereas an I-squared of 75% or more suggests considerable problems[42]. If I-squared is less than 40% we will consider the estimated effect to have a low degree of heterogeneity, but this will also be interpreted in light of the magnitude, direction of the effect, and its 95% confidence interval, sources of bias, and clinical significance [35,39,41,42].

Egger's statistics with 95% confidence intervals and associated funnel plot will depict potential publication or small sample bias related to our main outcome summaries and/or within subgroups [45]. Egger's test is based on the Galbraith plot which is a plot of difference over standard error against one over standard error. Egger suggests that a regression of study difference over standard error on 1/standard error be undertaken to test the null hypothesis that the intercept is equal to zero. If Egger's test is significant (p<.05), it means that the funnel plot is asymmetric and that smaller studies with smaller precision show larger effects sizes, suggesting bias. Sensitivity analyses will be pursued at minimum on high/low quality studies, on the use of un-validated standardised questionnaires, and use of structured clinical interviews. If enough studies are available, other factors that could influence our observed findings will be explored (e.g. sample size). Tabular and narrative descriptions will be offered for the studies which cannot be pooled into quantitative summaries due to differing metrics.

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 was informed by the lack of prior systematic reviews or meta-analyses exploring the outcomes of interest: prevalence of anxiety/depression in high/costly health care users and the magnitude of health care use associated with anxiety/depression across adult populations in any general medical settings.

DISCUSSION

The purpose of this systematic review is to estimate the prevalence of anxiety/depression in people who are frequent, high cost users of general health care services, and then, if possible, to estimate the level of health care use associated with the presence of anxiety/depression. While evidence is available suggesting that a small percentage of the population accrues high percentage of healthcare/costs, it is unclear to date to what extent the costs and use may be due to the presence of common mental health problems (depression/anxiety). By examining the information available to date we aim to describe the prevalence of anxiety/depression in people who are high/costly health care users, and where possible the magnitude of use and costs associated with these two common mental health problems.

Our review will build upon the recent systematic review by Wammes and colleagues [20] that described the characteristics of high-cost patients and found that a high prevalence of high cost patients had associated mental health disorders. This review will specifically focus upon depression/anxiety and include both studies of cost and health care use. It will also provide information about the prevalence of depression/anxiety in different health care settings, including primary care and ED. There is a trade-off between diagnostic accuracy versus size of study. Our results will complement those of Wammes and colleagues [20], and increase our understanding of the role of depression/anxiety in driving health care use and costs.

Strengths of this review are that it focuses upon common mental health problems, includes both studies of health care cost and health care use, and includes general health care settings, including primary, secondary care, and ED. Additional strengths are the inclusion of studies published in any language and the independent study identification, selection, and data extraction pursued by two independent reviewers.

IMPLICATIONS OF RESULTS

The results of this systematic review will provide an estimate of the prevalence of common mental health disorders in high users of health care services, while also providing an estimate of the magnitude of use associated with depression/anxiety. It will enable treatments, such as the collaborative care model, that have already been developed for the treatment of depression/anxiety in the physically ill, to be evaluated in high-cost patients with co-morbid depression/anxiety resulting in a more personalised approach to both treatment and policy.

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CONTRIBUTORS

OL and FJ developed the search strategy. OL 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. OL will be first reviewer and FJ will be second reviewer. All authors read and approved the manuscript.

COMPETING INTEREST

The authors declare that they have no competing interests.

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DATA SHARING AND STATEMENT

There are no unpublished data as this is a systematic review.

PATIENT CONSENT

Patient consent is not applicable as this is a protocol for a systematic review/meta-analysis.

ETHICS AND DISSEMINATION

As this systematic review will use data from existing studies no ethical approvals are warranted; the results will be published in a peer-reviewed publication and presented at relevant academic meetings.

Appendix 1:

Electronic search strategy in Medline used to conduct a comprehensive literature search.

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

Part 2: Cost/service utilisation	
41	high cost.mp.
42	high cost$.ti,ab,de.
43	high?cost$.ti,ab,de.
44	(high adj5 cost$).ti,ab,de.
45	frequent cost.mp.
46	frequent cost$.ti,ab,de.
47	(frequent adj5 cost$).ti,ab,de.
48	high expenditure.mp.
49	high expenditure.ti,ab,de.
50	(high adj5 expenditure).ti,ab,de.
51	high expense.mp.
52	high expense.ti,ab,de.
53	(high adj5 expense).ti,ab,de.
54	frequent user.mp.
55	frequent user.ti,ab,de.
56	(frequent adj5 user).ti,ab,de.
57	high user.mp.
58	high user.ti,ab,de.
59	(high adj5 user).ti,ab,de.
60	high utiliser.mp.
61	high utiliser$.ti,ab,de.
62	high utilizer.mp.
63	high utilizer$.ti,ab,de.
64	(high adj5 utiliser$).ti,ab,de.
65	(high adj5 utilizer$).ti,ab,de.
66	frequent utiliser.mp.
67	frequent utilizer.mp.
68	frequent utilizer$.ti,ab,de.
69	frequent utiliser$.ti,ab,de.
70	(frequent adj5 utilizer$).ti,ab,de.
71	(frequent adj5 utiliser$).ti,ab,de.
72	high utilisation.mp.
73	high utilization.mp.
74	high utilization.ti,ab,de.
75	high utilisation.ti,ab,de.
76	(high adj5 utilization).ti,ab,de.
77	(high adj5 utilisation).ti,ab,de.
78	frequent utilisation.mp.
79	frequent utilization.mp.
80	frequent utilisation.ti,ab,de.
81	frequent utilization.ti,ab,de.
82	(frequent adj5 utilisation).ti,ab,de.

83	(frequent adj5 utilization).ti,ab,de.
84	high need.mp.
85	high need.ti,ab,de.
86	(high adj5 need).ti,ab,de.
87	high attend.mp.
88	high attend$.ti,ab,de.
89	(high adj5 attend$).ti,ab,de.
90	superutilizer.mp.
91	superutilizer.ti,ab,de.
92	exp health expenditures/
93	exp patient acceptance of health care/
94	exp health care costs/
95	exp health services accessibility/
96	exp cost benefit analysis/
97	exp practice patterns physicians/
98	exp efficiency organizational/
99	exp health services misuse/
100	exp patient care team/
101	exp case management/
102	exp office visits/
103	exp referral/
Part 3: Anxiety/Depression terms	
104	exp anxiety/
105	(anxiety adj5 disorder$).tw
106	exp panic disorder/
107	(panic adj5 disorder$).tw
108	panic.tw
109	(panic adj5 attack$).tw
110	fear.tw
111	exp depression/
112	(depressive adj5 disorder$).tw

Appendix 2 - Data extraction form adapted from the framework of Hayden et al.

Eligibility criteria for the title and abstract screening phase

Inclusion criteria

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] Adults aged ≥ 18 years [2] Patients are high users of health care [2] Patients accrue high health care costs Including: high cost patients, high users, distressed high users/utilisers of care, frequent attenders in primary care, secondary care, frequent attenders at an emergency department **NB:** Please answer YES if patients with anxiety/depression are a subgroup; please answer YES if mixed age population.	Yes No Unclear	
Comparators		
[1] Comparison group includes non-high use OR non-high cost patients [2] Comparison group includes frequent/high users without anxiety/depression	Yes No Unclear	
Outcome		
Did the study report any of the following outcomes: [1] Prevalence of anxiety/depression in high users/high cost patients [2] Odds Ratio of use of care between depressed/anxious vs non-depressed/anxious participants	Yes No Unclear	
Final decision (please tick)	Include Exclude Unclear	

Exclusion criteria

Reasons for exclusion of study from review (please circle where appropriate)	
Study design	[1] Clinical trial [2] Case study [3] Qualitative study
Population	Age: <18 All specific medical specialties/illnesses including: [1] Paediatric patients [2] Palliative care [3] Obstetrics [4] Transplant [5] Neurodegenerative disease [6] Oral, maxillofacial, dentistry [7] Nephrology [8] Infectious diseases [9] Virology and HIV/AIDS [10] Physiotherapy [11] Cosmetic surgery

	[12] Psychiatry/mental health services [13] Specific diseases e.g. diabetes, cardiovascular
Intervention	[1] Randomised clinical trial [2] Interventions in populations who are not high use/cost [3] Screening/diagnosis/treatment evaluations
Comparator	Studies without non-high cost/non-high users of health care
Outcomes	Relevant outcomes not assessed: [1] No anxiety/depression assessment [2] No assessment of health use OR cost
Other	Duplicate publication Other (explain)

Eligibility criteria for Full Text	
Satisfaction of eligibility criteria above	Yes No Unclear
Cost studies will include patients either in the top 1%, 5% 10% and 20% of most costly patients.	**Yes** **No** **Unclear**
Studies of general health care use will include patients in the top 1%, 5%, 10% or 20% of health care use.	**Yes** **No** **Unclear**
Studies in primary care will either include patients with 10 or more visits per year or those patients in the top 10% of use	**Yes** **No** **Unlcear**
Studies of ED will include patients with at least 4 visits per annum.	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/Exclude without listing/Exclude with listing Other – please specify			
Notes				

Data extraction template for full-text articles

General study characteristics	
Location of study Please specify country, type of health care system, health care setting (primary/secondary care/ED/all settings)	
Study aims	Reported/Not reported
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 (standard deviation):#
Outcome definition	[1] Anxiety or depression or both Median (range):# Mean (standard deviation):# [2] Health care use Median (range):# Mean (standard deviation):# [3] Health care cost Median (range):# Mean (standard deviation):#
Outcome measurement	Did the study report measurements for any of the following outcomes: [1] Prevalence of anxiety/depression ➢ Specify measures of central tendency and variation) ➢ Specify instrument and range (e.g. PHQ-9, GAD-7, SCID, etc.) ➢ Is it self-report? ➢ Is it standardised? ➢ Is it validated to context? ➢ Is it a standardised clinical interview ➢ Is it a clinical interview with diagnosis according to recognised diagnostic system [2] Magnitude of cost or use of health care associated with the presence of anxiety/depression. Consider: ➢ Frequency and range of scheduled contacts in primary care, secondary care or ED ➢ Cost, range, of contacts in above settings ➢ Frequency and range of inpatient admissions ➢ Cost, range, currency of inpatient admissions
Covariates/Confounders considered (please detail)	[1] Did the study report measurements used to report: ➢ Patient characteristics and contexts associated with high service use/costs among patients with anxiety depression? *Please consider patient demographic (e.g. age, ethnicity, gender, homelessness) and clinical factors (e.g. anxiety/depression management, physical co-morbidities)*
Relationship between outcome and relevant covariates/confounders	Is the relationship statistically significant? Yes/No *If Yes:* OR/mean difference (95% confidence intervals):# *If No, offer reason:* Low powered or inconclusive study A true negative study

	Other reasons (please specify)
Power calculation	Yes/No/Not reported Calculated sample size:# Sample size achieved: Yes/No
Funding	Unclear Not reported Please state where reported
Conflict of interest statement	Yes/No/Not reported

Observational study characteristics	
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 groups comparable	Yes/No If No, please specify
Any confounders considered?	Yes/No If Yes, specify which If No, please specify
Analyses	
Drop-outs stated	Yes/No If Yes: number in each group

Patient characteristics			
Notes: Any relationship with outcomes? Yes/No/Not reported *If Yes,* please state statistical parameters and significance level where appropriate	Exposure (i.e. High use/cost)	Control (Low use/cost)	Comments
Number of patients			
Country			
Age mean/median (standard deviation/range)			
Ethnicity (Number, %)			
Sex (Number, %)	Male: Female:	Male: Female:	
Homelessness specified in study? Yes/No			
No of patients recruited			
No of patients allocated			
No of patients evaluated			
No of drop-outs			
Reasons for drop-out			
Definition of anxiety/depression in the groups:			

[1] Via standardised questionnaire (validated or not) semi-structured or clinical interview? *Please specify* [2] Definition of high/low ranges or diagnosis (yes/no) [3] Is anxiety/depression managed? Yes/No			
Clinical status at recruitment : [1] Comorbidities Yes/No *If yes, please state* Number:			
Adverse event? Yes/No *If Yes, please detail*			

Outcome details

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

Outcome assessed	
Definition of each outcome	
Time of assessment of each outcome	
Timing of assessment	
Length of follow up for each outcome	
Method of measurement	
No of patients evaluated for each outcome, as stated above	
Confounding variables were considered (e.g. age, gender, ethnicity, homelessness, physical co-morbidities, managed depression) *Please list all*	
How were the confounding variables controlled?	

Methodological quality summary					
Reviewer/Date:			Checked by:		
Contents (please refer to tables below for guidance	Yes	Partly	No	Unsure	Comments
Study participation					
Study attrition					
Measurement of outcome					
Analytical approach					
Specify confounding variables measurements (e.g. age, gender, ethnicity, homelessness, physical co-morbidities, managed depression)					

Specify method of controlling for confounding variables					
Summary	Low risk of bias		Moderate risk of bias		High risk of bias
Remarks:					

Appendix 3

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, anxiety/depression) [2] Was inclusion/exclusion assessed using valid and reliable measures? (for example, clinical interview to ascertain anxiety/depression 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 ➢ Homelessness (yes/no) ➢ Suitable definition of anxiety/depression	
Valid method for evaluating outcome	[1] Was there a definition provided for the key outcomes: ➢ Anxiety/depression caseness or diagnosis ➢ Health care use level and range ➢ Health care costs and range [2] Was there a method used to ascertain anxiety/depression clearly defined? ➢ Standardised questionnaires validated to the setting ➢ Standardised questionnaire not validated for the setting ➢ Clinical interview based on the ICD or DSM (version specified) ➢ Semi-structured research interview based on ICD or DSM version specified [3] Was a valid and reliable measure used to report outcomes? For example ➢ Frequency/range of health care use ➢ Mean/variation/currency of health care cost ➢ Clinical interview/Questionnaire score/variation	
Adequate follow-up period *(where applicable)*	[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 *(where applicable)*	[1] Were drop-out rates and reasons for drop-out similar across exposed and unexposed? [2] Were numbers of drop-outs/withdrawals documented at each time point?	
Analysis and control of confounders	[1] Does the study identify any confounders? [2] Does the study control for these confounders?	
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? (i.e. mean change)	
Analytical methods appropriate	[1] Was the type of analysis appropriate for the type of outcome data? For example:	

	➢ Continuous – Mixed model, ANCOVA ➢ Categorical - Mixed model for categorical outcome ➢ Dichotomous – Logistic regression [2] Was loss to follow-up accounted for in the analysis (e.g. through sensitivity analysis)	

Abbreviations

PROSPERO: Prospective Registering of Systematic Reviews; CINAHL: Cumulative Index for Nursing and Allied Health Literature; NHS: National Health Service; GP: General Practitioner; ED: Emergency Department; ANCOVA: Analysis of Covariance; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; NOS: The Newcastle – Ottawa Scale; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalised Anxiety Disorder Assessment-7; SCID: Structured Clinical Interview for DSM; ICD: International Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	3
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	N/A

		protocol amendments	
Sources	[#5a]()	Indicate sources of financial or other support for the review	19
Sponsor	[#5b]()	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	[#5c]()	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	[#6]()	Describe the rationale for the review in the context of what is already known	5
Objectives	[#7]()	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	[#8]()	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	[#9]()	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	[#10]()	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records - data management	[#11a]()	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	[#11b]()	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	[#11c]()	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	[#12]()	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9