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# BMJ Open

## Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

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# Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

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# Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

## Abstract

*Introduction.* Evidence from longitudinal single studies suggests that anxiety and depression may impact quality of life. However, systematic reviews synthesizing current evidence have mainly focused on specific samples. Thus, the aim of this study is to synthesize evidence on the association between anxiety, depression and quality of life from longitudinal studies in a systematic review.

*Methods and Analysis.* A systematic review of evidence from longitudinal studies analyzing the association between anxiety, depression and quality of life will be conducted, taking into account the current Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Several electronic databases from relevant fields of research will be searched (PubMed, PsycINFO, PSYINDEX, EconLit, NHS EED) using defined search terms. Moreover, reference lists of included studies will be searched manually. Study eligibility will be appraised in a two-step process against pre-defined inclusion/exclusion criteria. Primarily, information on study design and assessment, statistical methods, participant characteristics as well as results regarding our research question of interest will be extracted. The quality of included studies will be assessed using an appropriate tool. Study selection, data extraction and assessment of study quality will be performed by two reviewers. Disagreements will be resolved through discussion or by inclusion of a third party. Results will be synthesized narratively in text and tables. Depending on the number and heterogeneity of the studies included, a meta-analysis will be performed.

*Ethics and Dissemination.* As no primary data will be collected, approval from an ethics committee is not required. Results will be disseminated through conference presentations and publication in a peer-reviewed, scientific journal.

Registration. PROSPERO registration number: CRD42018108008

Keywords: anxiety, depression, quality of life, longitudinal studies, systematic review.

## Strengths and Limitations of the Study

- To our knowledge, this is the first systematic review synthesizing and critically assessing evidence from longitudinal, observational studies on the association between anxiety, depression and quality of life.
- The study's focus on longitudinal evidence from observational studies should strengthen the conclusions drawn from our results and may facilitate causal inference across studies.
- Two independent reviewers are involved in the processes of study selection, data extraction and quality assessment.
- Due to the possible heterogeneity between studies, conducting a meta-analysis might not be appropriate.

## 1. INTRODUCTION

Anxiety and depression are among the most prevalent mental health problems across all age categories<sup>1-3</sup>. Both disorders have been associated with a considerable economic burden<sup>4-6</sup>, as well as adverse implications for the affected individual, such as increased risk for physical comorbidities e.g. cardiovascular disease<sup>7 8</sup>. Moreover, individual cross-sectional and longitudinal studies have suggested that anxiety and depression are related to a reduced quality of life<sup>9-12</sup>.

There are several systematic reviews that have analyzed the association between anxiety and/or depression and quality of life previously. However, existing reviews are limited with respect to the samples analyzed. For example, some reviews have focused on certain age categories<sup>13 14</sup>, or samples with specific diseases<sup>15 16</sup>. Specifically, Creighton, et al.<sup>13</sup> as well as Sivertsen, et al.<sup>14</sup> have analyzed the association between anxiety or depression and quality of life in older people. Regarding reviews of disease-specific samples, Blakemore, et al.<sup>15</sup> have analyzed the association between anxiety, depression and quality of life in patients with chronic obstructive pulmonary disease, and Schram, et al.<sup>16</sup> have focused on depression and quality of life in patients with diabetes. In addition to this, previous reviews have tended to focus on the longitudinal association between quality of life and depression, rather than on anxiety.

To the best of our knowledge, there are no recent systematic reviews specifically analyzing evidence from longitudinal, observational studies on the association between anxiety, depression and quality of life across all age categories. To add to the present literature, we aim to synthesize current evidence on this association as well as assess the quality of existing studies.

### Objective

This paper provides the protocol for a systematic review that aims to synthesize and critically appraise longitudinal, observational studies assessing the association between anxiety, depression and quality of life. The studies of interest are those analyzing participants from all age categories with anxiety/depression, as well as those that include samples without a specific disease or receiving a specific intervention, applying valid measures for the main variables.

## 2. METHODS AND ANALYSIS

This systematic review protocol was developed taking into account the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines<sup>17</sup>. The study is registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42018108008, under <https://www.crd.york.ac.uk/PROSPERO/>).

### Eligibility criteria

Studies will be assessed for inclusion according to the inclusion/exclusion criteria outlined below. Before the final eligibility criteria are applied, they will be tested against a sample of 100 titles/abstracts and refined should further clarification be required.

#### Inclusion criteria:

- observational studies analyzing the longitudinal association between anxiety or depression (including disorders as well as symptom severity) and quality of life across all age categories
- studies analyzing samples with anxiety/depression or samples without a specific disease (other than anxiety/depression)
- studies applying an appropriate measure for anxiety and depression (e.g. psychiatric diagnosis according to criteria of the International Classification of Diseases (ICD), the Diagnostic and Statistical Manual of Mental Disorders (DSM), or using a valid screening tool)
- studies applying an appropriate measure for quality of life (e.g. the 36-item Short Form Health Survey)
- publications in German or English language, published in peer-reviewed journals

#### Exclusion criteria:

- studies not focusing on the association between anxiety or depression and quality of life over time

- studies only analyzing disease-specific samples (meaning conditions other than anxiety/depression) or samples receiving specific interventions
- study design other than observational
- assessment of anxiety, depression or quality of life not appropriate
- studies not published in peer-reviewed journal or in language other than German or English

## Information sources and search strategy

As quality of life is an outcome analyzed in several fields of research, such as medicine, psychology, and health economics, several databases from multiple scientific fields (PubMed, PsycINFO, PSYINDEX, EconLit, NHS EED) will be searched electronically.

The electronic database search will be conducted using predefined search terms, including *anxiety disorder*, *depressive disorder*, *anxi\**, *depress\** (truncated to also capture studies using terms such as *anxious* or *depressed*), *quality of life*, and *longitudinal study*. The draft of the PubMed search is provided in table 1. There will be no restriction on location or time of the publication. If possible, search terms will be entered as Medical Subject Headings (MeSH), or keywords in the title/abstract. If needed, the search will be modified according to the specific requirements of each database.

Additionally, the reviewers will search the reference lists of included articles for relevant articles.

Table 1. Draft PubMed search strategy

	Term entered
#1	anxi*[Title/Abstract] OR depress*[Title/Abstract]
#2	Anxiety Disorder[MeSH]
#3	Depressive Disorder[MeSH]
#4	#1 OR #2 OR #3
#5	Quality of Life[MeSH]
#6	Longitudinal studies[MeSH]
#7	(#4 AND #5 AND #6)



## Data management

All records retrieved in the database search will be imported into the literature management software EndNote to facilitate the management of the references. Should it be possible to conduct a meta-analysis, Stata (StataCorp, College Station, Texas) will be used for the quantitative analysis.

## Study selection process

All studies obtained in the electronic and manual search will be assessed for inclusion/exclusion in a two-step process (1. title/abstract screening, 2. screening of full texts). Before the final selection criteria are applied, the criteria will be pre-tested against a sample of 100 titles/abstracts and, if necessary, refined afterwards. The study selection process will be conducted independently by two reviewers (JKH, EQ) using the previously defined and refined selection criteria. Disagreements between the two reviewers will be resolved through discussion or by inclusion of a third party (AH).

## Data collection process and data items

The data extraction process will involve two reviewers as well (JKH, EQ). One reviewer will extract relevant data items from the studies in standardized form, and the second reviewer will cross-check the extracted data. Again, in case of disagreements consensus will be reached through discussion or by inclusion of a third party (AH). In cases where relevant data cannot be extracted or require clarification, the authors of the study will be contacted.

Data items to be extracted from the original studies include information on study design, definition and assessment of the main variables of interest, sample characteristics, statistical methods, as well as results regarding the longitudinal association between anxiety, depression and quality of life.

## Assessment of study quality/risk of bias

The quality of the individual studies will be assessed using a quality assessment tool appropriate for longitudinal, observational studies, such as the Newcastle-Ottawa Scale<sup>18</sup> or the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies<sup>19</sup>. For example, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies comprises of 14 quality criteria to assess the internal validity of a study, through consideration of potential forms of bias.

Each study included in the final synthesis will be appraised for study quality by two reviewers (JKH, EQ) independently. Should there be disagreement, consensus will be reached through discussion or by inclusion of a third party (AH). Results from the quality assessment will be included in the study synthesis.

## Data synthesis

Following its completion, the study selection process will be illustrated by means of a PRIMSA flowchart. The results from data extraction and quality assessment processes will be synthesized qualitatively in text and tables. If possible, results will be categorized according to specific disorder/symptoms analyzed in the studies (anxiety/depression) or outcome domain analyzed (quality of life measure).

Egger, et al.<sup>20</sup> advise caution when conducting meta-analyses to pool results specifically from observational studies, as this may result in precise but incorrect estimates, due to confounding and bias within the included studies. However, recommendations on conducting a meta-analysis on data from observational studies vary, and to date there is no agreed upon, comprehensive methodological outline for such analyses. For the most part, current recommendations center around whether to, and how one should, pool the data<sup>21</sup>. Whether a meta-analysis is performed (in view of the number of studies included as well as their heterogeneity) in our study, and how the analysis is conducted (i.e. method used for the standardization of the outcome measure as well as statistical methods for calculation of the overall effect), will be discussed in the final systematic review, with reference to current recommendations.

Thus, only if appropriate, a meta-analysis will be performed to obtain a pooled, quantitative estimate. Moreover, if a meta-analysis can be performed and a sufficient number of studies can be included in the synthesis, we plan to perform subgroup analyses (e.g. by gender, age) or sensitivity analyses (e.g. excluding

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3 studies with lower quality/higher risk of bias) to explore possible sources of heterogeneity as well as check  
4 the robustness of the results.  
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### 10 3. DISCUSSION 11 12

13 This systematic review will provide an overview of evidence from longitudinal, observational studies on  
14 the association between anxiety, depression and quality of life across all age categories. Moreover, the  
15 quality of included studies will be rated. If possible, data will be pooled quantitatively by means of a meta-  
16 analysis, and subgroup or sensitivity analyses will be performed.  
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21 As stated in the introduction, this review adds to the present literature by additionally including samples  
22 without a specific disease (e.g. general population samples) and not focusing on a specific age category.  
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25 Beyond providing an overview of evidence on the association between anxiety, depression and quality of  
26 life, and thus highlighting possible gaps in current research, there are a range of questions that could  
27 possibly be answered with this review. For example, it could be demonstrated whether specific quality of  
28 life domains are particularly affected by specific disorders or symptoms across studies. Furthermore, if  
29 studies show different results, possible sources of heterogeneity could be assessed across studies.  
30 Heterogeneity might be due to study design and methodology as well as due to sample-specific  
31 characteristics. Moreover, subgroups, such as age group or gender, could be analyzed.  
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38 Finally, longitudinal evidence has several advantages over cross-sectional data. For example, trajectories  
39 over time can be analyzed within the same individuals. Moreover, applying appropriate methods in  
40 longitudinal analysis can take intraindividual heterogeneity into account, which is a key point in the  
41 analysis of QoL<sup>22</sup>. Thus, as it draws from longitudinal evidence across several studies, our systematic  
42 review provides the basis for stronger, more definitive conclusions that one would be not be able to draw  
43 from a single study.  
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### 52 Strengths and limitations 53 54

55 To our knowledge, this is the first study aiming to synthesize and critically appraise evidence from  
56 longitudinal, observational studies analyzing the association between anxiety, depression and quality of  
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3 life across all age categories. Focusing on observational studies and samples without a specific illness  
4 (other than anxiety or depression), should limit the influence of a specific intervention, treatment or  
5 disease on the association between anxiety, depression and quality of life. In turn, this should strengthen  
6 the conclusion we can draw from our results. Moreover, another strength is the inclusion of two  
7 independent reviewers in the processes of study selection, data extraction, and quality assessment. One  
8 limitation is that conducting a meta-analysis may not be appropriate due to heterogeneity of existing  
9 studies. Thus, it may not be possible to obtain a pooled estimate.  
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## 19 Ethics and dissemination

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21 As no primary data will be collected, approval by an ethics committee is not required. The results from the  
22 systematic review are planned to be published in a peer-reviewed journal and presented at scientific  
23 conferences.  
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## Authors' contributions

The study concept was developed by JKH, HHK and AH. The manuscript of the protocol was drafted by JKH and critically revised by HHK, EQ and AH. The draft search strategy was developed by JKH and AH. Study selection, data extraction and quality assessment will be performed by JKH and EQ, with AH as a third party in case of disagreements. All authors have approved the final version of the manuscript.

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## Competing interests statement

The authors declare no conflict of interest.

## Word count

1,859 words

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 1 (title)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (not an update)
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 2 (abstract), p. 5 (methods)
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 11 (authors' contributions)
<b>Amendments</b>	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 protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no amendment)
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 12 (funding statement)
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no specific funding received)
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no specific



Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
					funding received)
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 4 (introduction)
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 4ff (objective, methods)
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 5f (eligibility criteria)
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 6f (information sources and search strategy)
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 6f (information sources and search strategy)
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data management)
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (study selection process)
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)



Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)
<b>Risk of bias in individual studies</b>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7f (assessment of study quality/risk of bias)
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
	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 (e.g., $I^2$ , Kendall's tau)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See p. 8 (data synthesis) for exploration
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no trials/intervention studies with possible protocols included; no grey literature included to check for these sorts of bias)
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (not sure whether meta-analysis is possible; moreover, no

Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
					intervention studies analysed and thus no treatment/policy recommendations planned)

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# BMJ Open

## Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

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Keywords:	anxiety, depression, quality of life, longitudinal studies, systematic review

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# Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

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# Association between anxiety, depression and quality of life - Study protocol for a systematic review of evidence from longitudinal studies

## Abstract

*Introduction:* Evidence from individual longitudinal studies suggests that anxiety and depression may impact quality of life. However, systematic reviews synthesizing current evidence have mainly focused on specific samples. Thus, the aim of this study is to synthesize evidence from longitudinal studies on the association between anxiety, depression and quality of life in a systematic review.

*Methods and Analysis:* A systematic review of evidence from longitudinal studies analyzing the association between anxiety, depression and quality of life will be conducted, taking into account the current Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Several electronic databases from relevant fields of research (PubMed, PsycINFO, PSYINDEX, EconLit, NHS EED) will be searched in September 2018 using defined search terms, with an updated search planned. Moreover, reference lists of included studies will be searched manually. Study eligibility will be appraised in a two-step process against pre-defined inclusion/exclusion criteria. Primarily, information on study design and assessment, statistical methods, participant characteristics as well as results regarding our research question will be extracted. The quality of included studies will be assessed using an appropriate tool. Study selection, data extraction and assessment of study quality will be performed by two reviewers. Disagreements will be resolved through discussion or by inclusion of a third party. Results will be synthesized narratively in text and tables. Depending on the number and heterogeneity of the studies included, a meta-analysis will be performed.

*Ethics and Dissemination:* As no primary data will be collected, approval from an ethics committee is not required. Results will be disseminated through conference presentations and publication in a peer-reviewed, scientific journal.

*Registration:* PROSPERO registration number: CRD42018108008

*Keywords:* anxiety, depression, quality of life, longitudinal studies, systematic review.

## Strengths and Limitations of the Study

- To our knowledge, this is the first systematic review synthesizing and critically assessing evidence from longitudinal, observational studies on the association between anxiety, depression and quality of life, focusing on samples without specific disorders.
- The study's focus on longitudinal evidence from observational studies should strengthen the conclusions drawn from our results and may facilitate causal inference across studies.
- Two independent reviewers are involved in the processes of study selection, data extraction and quality assessment.
- Due to the possible heterogeneity between studies, conducting a meta-analysis may not be appropriate.

## 1. INTRODUCTION

Anxiety and depression are among the most prevalent mental health problems across all age categories<sup>1-3</sup>. Both disorders have been associated with a considerable economic burden<sup>4-6</sup>, as well as adverse implications for the affected individual, such as increased risk for physical comorbidities, e.g. cardiovascular disease<sup>7,8</sup>. Moreover, individual cross-sectional and longitudinal studies have suggested that anxiety and depression are related to a reduced quality of life in samples with and without specific diseases<sup>9-12</sup>.

There are several systematic reviews that have synthesized evidence on the association between anxiety and/or depression and quality of life previously. However, existing reviews are limited with respect to the samples analyzed. For example, some reviews have focused on certain age categories<sup>13</sup>,<sup>14</sup>, or samples with specific diseases<sup>15,16</sup>. Specifically, Creighton, et al.<sup>13</sup> as well as Sivertsen, et al.<sup>14</sup> have analyzed the association between anxiety or depression and quality of life in older people. Regarding reviews of disease-specific samples, Blakemore, et al.<sup>15</sup> have analyzed the association between anxiety, depression and quality of life in patients with chronic obstructive pulmonary disease (COPD), and Schram, et al.<sup>16</sup> have focused on depression and quality of life in patients with diabetes. Looking at longitudinal studies in particular, most reviews find a negative association with varying strength of the association. For example, the meta-analysis conducted by Blakemore, et al.<sup>15</sup> in patients with COPD found, that depression and anxiety were significantly related to reduced health-related quality of life at follow-up with moderate to large effect sizes. In contrast, Schram, et al.<sup>16</sup> reported no to small, negative effects of depressive symptoms on domain-specific quality of life in samples of patients with diabetes.

To the best of our knowledge, there are no recent systematic reviews specifically analyzing evidence from longitudinal studies on the association between anxiety, depression and quality of life across all age categories and focusing on samples without specific diseases or disorders (other than anxiety or depression). Looking at longitudinal studies in particular provides the advantage that individual trajectories can be observed over time and thus, temporal associations between the variables can be assessed. Moreover, focusing on observational studies analyzing samples without specific diseases means the effects of interventions or specific illnesses will be limited in terms of impact on this association.

Thus, to add to the present literature, we aim to synthesize current longitudinal, observational studies on the association between anxiety, depression and quality of life, as well as assess the quality of existing studies.

## Objective

This paper provides the protocol for a systematic review that aims to synthesize and critically appraise longitudinal, observational studies assessing the association between anxiety, depression and quality of life. The studies of interest are those analyzing participants from all age categories with anxiety/depression, as well as those that include samples without a specific disease or receiving a specific intervention, applying valid measures for the main variables.

## 2. METHODS AND ANALYSIS

This systematic review protocol was developed taking into account the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines<sup>17</sup>. The study is registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42018108008, under <https://www.crd.york.ac.uk/PROSPERO/>).

### Eligibility criteria

Studies will be assessed for inclusion according to the inclusion/exclusion criteria outlined below. Before the final eligibility criteria are applied, they will be tested against a sample of 100 titles/abstracts and refined should further clarification be required.

#### Inclusion criteria:

- observational studies analyzing the longitudinal association between anxiety/depressive symptoms or disorder and quality of life across all age categories (to analyze the association with quality of life according to severity of anxiety/depressive symptoms as well as for those who fulfill the criteria for a clinical diagnosis)
- studies analyzing samples with anxiety/depression or samples without a specific disease (other than anxiety/depression)
- studies applying an appropriate measure for anxiety and depression (e.g. psychiatric diagnosis according to criteria of the International Classification of Diseases (ICD), the Diagnostic and



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3 Statistical Manual of Mental Disorders (DSM), or using a valid self-report screening  
4 questionnaire, such as the depression scale from the Patient Health Questionnaire (PHQ-9) or  
5 the Hospital Anxiety and Depression Scales (HADS))  
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8 - studies applying an appropriate measure for quality of life (e.g. the 36-item Short Form Health  
9 Survey)  
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11 - publications in German or English language, published in peer-reviewed journals  
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#### 17 Exclusion criteria:

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19 - studies not focusing on the association between anxiety or depression and quality of life over  
20 time  
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22 - studies only analyzing disease-specific samples (meaning conditions other than  
23 anxiety/depression) or samples receiving specific interventions  
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25 - study design other than observational  
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27 - assessment of anxiety, depression or quality of life not appropriate (e.g. for anxiety/depression  
28 not according to ICD/DSM criteria or no valid, self-report screening questionnaire)  
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30 - studies not published in peer-reviewed journal or in language other than German or English  
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#### 37 Information sources and search strategy

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40 As quality of life is an outcome analyzed in several fields of research, such as medicine, psychology,  
41 and health economics, several databases from multiple scientific fields (PubMed, PsycINFO, PSYINDEX,  
42 EconLit, NHS EED) will be searched electronically in September 2018. It is planned to update the search  
43 prior to the submission of the final review to ensure that it contains the most recent evidence. The  
44 electronic database search will be conducted using predefined search terms, including *anxiety*  
45 *disorder*, *depressive disorder*, *anxi\**, *depress\** (truncated to also capture studies using terms such as  
46 *anxious* or *depressed*), *quality of life*, and *longitudinal study*. The PubMed search strategy is provided  
47 in table 1. There will be no restriction on location or time of the publication. Where possible, search  
48 terms will be entered as Medical Subject Headings (MeSH), or keywords in the title/abstract. As  
49 needed, the search will be modified according to the specific requirements of each database.  
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57 Additionally, the reviewers will search the reference lists of included articles for further relevant  
58 articles.  
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Table 1. PubMed search strategy

	Term entered
#1	anxi*[Title/Abstract] OR depress*[Title/Abstract]
#2	Anxiety Disorder[MeSH]
#3	Depressive Disorder[MeSH]
#4	#1 OR #2 OR #3
#5	Quality of Life[MeSH]
#6	Longitudinal studies[MeSH]
#7	(#4 AND #5 AND #6)

## Data management

All records retrieved in the database search will be imported into the literature management software EndNote to facilitate the management of the references. Should it be possible to conduct a meta-analysis, Stata (StataCorp, College Station, Texas) will be used for the quantitative analysis.

## Study selection process

All studies obtained in the electronic and manual search will be assessed for inclusion/exclusion in a two-step process (1. title/abstract screening, 2. screening of full texts). Before the final selection criteria are applied, the criteria will be pre-tested against a sample of 100 titles/abstracts and, if necessary, refined afterwards. The study selection process will be conducted independently by two reviewers (JKH, EQ) using the previously defined and refined selection criteria. Disagreements between the two reviewers will be resolved through discussion or by inclusion of a third party (AH).

## Data collection process and data items

The data extraction process will involve two reviewers as well (JKH, EQ). One reviewer will extract relevant data items from the studies in standardized form, and the second reviewer will cross-check the extracted data. Again, in case of disagreements consensus will be reached through discussion or

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3 by inclusion of a third party (AH). In cases where relevant data cannot be extracted or require  
4 clarification, the authors of the study will be contacted.  
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7 Data items to be extracted from the original studies include information on study design, definition  
8 and assessment of the main variables of interest, sample characteristics, statistical methods, as well  
9 as results regarding the longitudinal association between anxiety, depression and quality of life.  
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## 16 Assessment of study quality/risk of bias

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19 The quality of the individual studies will be assessed using a quality assessment tool appropriate for  
20 longitudinal, observational studies, such as the Newcastle-Ottawa Scale<sup>18</sup> or the Quality Assessment  
21 Tool for Observational Cohort and Cross-Sectional Studies<sup>19</sup>. For example, the Quality Assessment Tool  
22 for Observational Cohort and Cross-Sectional Studies comprises 14 quality criteria to assess the  
23 internal validity of a study, through consideration of potential forms of bias.  
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28 Each study included in the final synthesis will be appraised for study quality by two reviewers (JKH, EQ)  
29 independently. Should there be disagreement, consensus will be reached through discussion or by  
30 inclusion of a third party (AH). Results from the quality assessment will be included in the study  
31 synthesis.  
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## 39 Data synthesis

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42 Following its completion, the study selection process will be illustrated by means of a PRIMSA  
43 flowchart. The results from data extraction and quality assessment processes will be synthesized  
44 qualitatively in text and tables. If possible, results will be categorized according to specific  
45 disorder/symptoms analyzed in the studies (anxiety/depression) or outcome domain analyzed (quality  
46 of life measure).  
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51 Egger, et al.<sup>20</sup> advise caution when conducting meta-analyses to pool results specifically from  
52 observational studies, as this may result in precise but incorrect estimates, due to confounding and  
53 bias within the included studies. However, recommendations on conducting a meta-analysis on data  
54 from observational studies vary, and to date there is no agreed upon, comprehensive methodological  
55 outline for such analyses. For the most part, current recommendations center around whether to, and  
56 how one should, pool the data<sup>21</sup>. Whether a meta-analysis is performed (in view of the number of  
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3 studies included as well as their heterogeneity) in our study, and how the analysis is conducted (i.e.  
4 method used for the standardization of the outcome measure as well as statistical methods for  
5 calculation of the overall effect), will be discussed in the final systematic review, with reference to  
6 current recommendations.  
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10 Thus, only if appropriate, a meta-analysis will be performed to obtain a pooled, quantitative estimate.  
11 Moreover, if a meta-analysis can be performed and a sufficient number of studies can be included in  
12 the synthesis, we plan to perform subgroup analyses (e.g. by gender, age) or sensitivity analyses (e.g.  
13 excluding studies with lower quality/higher risk of bias) to explore possible sources of heterogeneity  
14 as well as check the robustness of the results.  
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### 23 Patient and public involvement statement

24 The present review protocol did not involve individual patients or public agencies.  
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### 30 3. DISCUSSION

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33 This systematic review will provide an overview of evidence from longitudinal, observational studies  
34 on the association between anxiety, depression and quality of life across all age categories. Moreover,  
35 the quality of included studies will be rated. If possible, data will be pooled quantitatively by means of  
36 a meta-analysis, and subgroup or sensitivity analyses will be performed.  
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41 As stated in the introduction, this review adds to the present literature by additionally including  
42 samples without a specific disease (e.g. general population samples) and not focusing on a specific age  
43 category.  
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47 Beyond providing an overview of evidence on the association between anxiety, depression and quality  
48 of life, and thus highlighting possible gaps in current research, there are a range of questions that could  
49 possibly be answered by this review. For example, our study could ascertain whether specific quality  
50 of life domains are particularly affected by specific disorders or symptoms across studies over time.  
51 Comer et al.<sup>9</sup> found in a cross-sectional analysis in the general population, that different anxiety  
52 disorders were associated with varying decrements in different health-related quality of life domains.  
53 If this type of finding were observed over several longitudinal studies in the course of our systematic  
54 review, our study could also inform clinical research. Identification of the specific domains impacted  
55 by anxiety/depression, for example, could act as the starting point for the analysis of treatment goals  
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3 or the analysis of the effectiveness of interventions aiming to improve quality of life. However, as  
4 intervention studies, such as randomized controlled trials, will not be included in our review, additional  
5 research would need to be undertaken to build on this further. In addition, if studies show different  
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7 results, possible sources of heterogeneity could be assessed across studies. Heterogeneity might be  
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9 due to study design and methodology as well as due to sample-specific characteristics. Moreover,  
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11 subgroups, such as age group or gender, could be analyzed.  
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14 Finally, longitudinal evidence has several advantages over cross-sectional data. For example,  
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16 trajectories over time can be analyzed within the same individuals. Moreover, applying appropriate  
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18 methods in longitudinal analysis can take intraindividual heterogeneity into account, which is a key  
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20 point in the analysis of quality of life<sup>22</sup>. Thus, as it draws from longitudinal evidence across several  
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22 studies, our systematic review provides the basis for stronger, more definitive conclusions that one  
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24 would not be able to draw from a single study.  
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## 28 Strengths and limitations

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31 To our knowledge, this is the first study aiming to synthesize and critically appraise evidence from  
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33 longitudinal, observational studies analyzing the association between anxiety, depression and quality  
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35 of life across all age categories. Focusing on observational studies and samples without a specific illness  
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37 (other than anxiety or depression), should limit the influence of a specific intervention, treatment or  
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39 disease on the association between anxiety, depression and quality of life. In turn, this should  
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41 strengthen the conclusion we can draw from our results. Moreover, another strength is the inclusion  
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43 of two independent reviewers in the processes of study selection, data extraction, and quality  
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45 assessment. One limitation is that conducting a meta-analysis may not be appropriate due to  
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47 heterogeneity of existing studies. Thus, it may not be possible to obtain a pooled estimate.  
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## 50 Ethics and dissemination

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53 As no primary data will be collected, approval by an ethics committee is not required. The results from  
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55 the systematic review are planned to be published in a peer-reviewed journal and presented at  
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57 scientific conferences.  
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## Authors' contributions

The study concept was developed by JKH, HHK and AH. The manuscript of the protocol was drafted by JKH and critically revised by HHK, EQ and AH. The search strategy was developed by JKH and AH. Study selection, data extraction and quality assessment will be performed by JKH and EQ, with AH as a third party in case of disagreements. All authors have approved the final version of the manuscript.

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## Competing interests statement

The authors declare no conflict of interest.

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Word count

2,223 words

For peer review only



## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 1 (title)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (not an update)
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 2 (abstract), p. 5 (methods)
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 11 (authors' contributions)
<b>Amendments</b>	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 protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no amendment)
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 12 (funding statement)
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no specific funding received)
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no specific funding received)
<b>INTRODUCTION</b>					

Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 4 (introduction)
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 4ff (objective, methods)
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 5f (eligibility criteria)
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 6f (information sources and search strategy)
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 6f (information sources and search strategy)
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data management)
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (study selection process)
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7 (data collection process and data items)
<b>Risk of bias in individual studies</b>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 7f (assessment of study quality/risk of bias)

Section/topic	#	Checklist item	Information reported		Page number(s)/ section
			Yes	No	
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
	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 (e.g., $I^2$ , Kendall's tau)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See p. 8 (data synthesis) for exploration
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	p. 8 (data synthesis)
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (no trials/intervention studies with possible protocols included; no grey literature included to check for these sorts of bias)
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable (not sure whether meta-analysis is possible; moreover, no intervention studies analysed and thus no direct treatment/policy recommendations planned)